CRANIOFACIAL PATTERN PROFILE ANALYSIS OF INDIVIDUALS WITH FRONTONASAL MALFORMATION

by

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INTRODUCTION

Working in Germany in 1859, I. Hoppe was probably the first to describe the clinical entity that would later be termed frontonasal malformation, FNM. Since that time, the disorder has been known by many pseudonyms: eine angeborene Spaltung der Nase, median cleft face syndrome, frontonasal syndrome, frontonasal dysplasia, craniofrontonasal dysplasia, and frontonasal malformation. The description of FNM consists of hypertelorism, broad nasal root, lack of a nasal tip, widow's peak, and anterior cranium bifidum occultum. Associated defects may include midline clefting of the nose and/or upper lip, rarely, the palate, and unilaterally or bilaterally, the nasal alae.

A considerable amount of information has been added to the clinical picture of the anomaly since Hoppe's original work. Although this anomaly is rare, it usually occurs sporadically as an isolated incident, yet FNM will manifest occasionally as a genetic contribution in some families. The typical facies is relatively similar for all patients affected with FNM, but the spectrum of severity is great, varying from almost undetectable to a face with partially duplicated features. In all, the common denominator is hypertelorism. The craniofacial cephalometric description of these patients has yet to be reported. There have been no studies performed to quantify and characterize this frontonasal malformation via the anatomic radiographic measurements of lateral (LA) and posterior-anterior (PA) films.

Fortunately, there are lateral (LA) and posterior-anterior (PA) cephalometric measurement standards published, derived from "normal," unaffected populations that have been established by many investigators. These measurement standards are reported in the literature and often provide a basis for scientific and statistical comparison for clinical and research purposes. In some studies, family members who are related to others only by marriage serve as the "normal" standard for comparative purposes. This obligate "normal" population is so defined because their chance of having genetic liability, otherwise known as empirical risk, for affected offspring is similar to that of the general population risk, a figure that is much smaller than what must be the risk for blood relatives of the anomaly -- assuming a genetic basis for that anomaly.

The purpose of the present study was to examine the LA and PA cephalometric headplates taken on patients affected with FNM to plot and determine the pattern profile of the anomaly. This addresses the preliminary research hypothesis that the lateral and posterior-anterior cephalometric radiographs of individuals with frontonasal malformation have anatomic features that are unusual and distinct to the specific malformation. Additional hypotheses were also addressed, i.e., is familial FNM different than the sporadic FNM? On the average, are familial cases less severely affected than sporadic cases? In essence, it is the aim of this project to describe the craniofacial characteristics of FNM. This information can then be used to describe the specific anomaly so that an explanation can begin of what factors determine a FNM patient's facial features.

REVIEW OF LITERATURE

TERMINOLOGY

According to Gorlin et al.[1], frontonasal malformation, FNM, was first described by Hoppe in 1859.[2] The anomaly is characterized by: (a) ocular hypertelorism, (b) broadening of the nasal root, (c) lack of formation of a nasal tip, (d) V-shaped hair prolongation onto the forehead (also known as widow's peak), (e) anterior cranium bifidum occultum, (f) median facial cleft affecting the nose or both the nose and the upper lip and, at times, the palate, (g) premature closure of the cranial sutures, and (h) uni- or bilateral clefting of the ala nasi.[3] The condition often presents clinically with highly variable expression. Bixler[4] contends that the incidence of FNM is one birth in approximately every 100,000 live births. Although anomaly is rare, it usually occurs sporadically as an isolated incident, yet FNM will manifest occasionally as a genetic contribution in some families.

Since 1859, FNM has been known by many pseudonyms. Hoppe[2] first described the face by the name "eine angeborene Spaltung der Nase," a German name when translated means an inborn split of the nose. In 1967, DeMyer[5] proposed the term "median cleft face syndrome," whereas Rosasco and Massa[6] in 1968 introduced the term "frontonasal syndrome." Sedano et al.[3] in 1970 recognized that the condition did not satisfy the definition of a syndrome (a symptom complex that is characterized by at least three signs and symptoms; a pattern of anomalies that are related

pathogenetically) and that it actually is a primary malformation. Malformations denote a primary and often intrinsic problem in morphogenesis of a tissue; these occur during embryogenesis, resulting in a morphological defect due to an abnormal developmental process.[7] Sedano et al. suggested that it is possibly the result of a dysplasia, an abnormal growth of tissue. As such, they coined the term "frontonasal dysplasia." In 1979, Cohen[8] introduced the term "craniofrontonasal dysplasia" when he reported a case of a young lady with frontonasal dysplasia and ocular hypertelorism. Frontonasal dysplasia is both etiologically and pathogenetically heterogeneous.[9] Jones[10] noted that defects and disorders that derive from migrational abnormalities primarily of cranial neural crest cells like frontonasal dysplasia represent true malformations. Furthermore, FNM is considered to be a nonspecific developmental field defect manifested by a midfacial malformation and a host of low-frequency anomalies, resulting in a wide variety of abnormalities. Based on this concept, Sedano and Gorlin[11] proposed the term "frontonasal malformation" in 1988.

Sedano and Gorlin[11] suggest that FNM follows the basic definitions of developmental field defects (DFDs). A developmental field refers to the part or parts of an embryo that react as a unit to stimuli. The developmental fields are considered temporary units because the dimensions and ability to react will change according to the embryological development of the fetus. The midline is an example of a developmental field defect with a high morphologic impact. The requirements of a DFD are: (1) DFDs are causally nonspecific primary malformations that are causally heterogeneous,

(2) DFDs are anomalies of incomplete formation mostly affecting the midline, (3) most DFDs can be components of syndromes or associations or may lack associated abnormalities, and (4) most DFDs are multifactorially determined, not inherited, and thus have a low recurrence risk. There is some contention that DFDs are not necessarily multifactorial. The alteration most likely occurs between days 21 and 70 of intrauterine life.[11] A DFD is etiologically heterogenous by definition. In FNM, the broad etiologic groups are given as chromosomal, chemical agents, and genetic. The term frontonasal malformation, FNM, will be used because it is in agreement with the DFD concept adopted for this entity.

EMBRYONIC FACIAL GROWTH

Before a pathologic growth pattern can be discussed, a complete understanding of normal facial growth must be recognized. An understanding of the normal events in the embryologic development of the face facilitates the study of a rare craniofacial cleft like FNM. A brief summary of the pertinent events, based on a synopsis by Kawamoto[12], follows.

The embryologic development of the face takes place between the fourth and eighth weeks of gestation. The midportion of the face develops immediately anterior to the forebrain by the differentiation of the broad frontonasal prominence. Thickened ectodermal plates, the nasal placodes, arise from either side of the frontonasal prominence just above the stomodeum. Progressive elevation of the mesoderm

at the margins of the placodes produces a horseshoe-shaped ridge, which is open inferiorly. The limbs of the placodes become the median and lateral nasal processes.[12]

The paired median nasal processes merge with the frontonasal prominence to form the major portion of the frontal process. These structures gradually enlarge to displace the frontonasal prominence in a cephalic direction. The median nasal processes coalesce in the midline during the sixth week. Their caudal prolongations, the globular processes, follow a similar pattern as they expand above the midportion of the stomodeum. The premaxilla, the philtrum of the upper lip, the columella, the nasal tip, the cartilaginous portion of the nasal septum, and the primary palate are derived from the paired median elements. Above them the frontonasal process persists and narrows to form the bridge and root of the nose. The lateral nasal processes form the alar region of the nose.[12] Interestingly, at this stage, the face is only a thin layer of tissue over a massive brain.

Johnston[13], in 1964, extirpated various segments of the chick neural crest and noted that malformations were closely related to that segment. The most severe facial malformations, those of the frontonasal process, resulted from the extirpation of the mid-brain neural crest. Later in 1985, Patterson and Minkoff[14] proposed that the nasal development of the chick embryo may be governed initially by the forebrain enlargement and associated lateral movements of mesenchyme in the medial nasal processes, resulting in reorientation of the invaginating nasal placodes; subsequently, orbital enlargement and an associated medial direction of growth of the lateral nasal

processes assumes greater significance to the continued development of the frontonasal region.

The embryopathogenesis of the craniofacial region is extremely complex. During a four week period, an extreme demand is placed on the coordination of cell separation, migration, and interaction. The proper amount of tissue must be present at an exact moment in the correct three-dimensional relationship. Precise movement and timing are critical. Any mishap can lead to disastrous consequences. The resulting chasm usually falls along predictable embryonic lines. Various theories have been proposed to explain the formation of clefts.

THEORIES OF FACIAL CLEFT FORMATION

Two leading theories of facial cleft formation exist, according to Kawamoto.[12] The classic theory, proposed by Dursy[15] and His[16], states that failure of fusion of the facial processes is responsible for the development of clefts. This idea was questioned by Pohlmann[17] and Veau and Politzer[18] as the theory of mesodermal migration and penetration began to emerge. The investigations of Stark[19] also supported this challenge. Although most of the present knowledge is based on the study of cleft lip and palate morphogenesis in nonhuman embryos, Kawamoto[12] states that "it is highly probable that rare craniofacial clefts are produced by similar mechanisms."

The classic concept of fusion pictures the central region of the face as the site of union of the free ends of the facial processes. The

face begins to take form as its various processes fuse. After epithelial contact is established, penetration by the mesoderm occurs to complete the fusion and the formation of the anatomic structure.[20] Disruption of this sequence leads to the formation of a cleft.[21]

There are many voids that remain in the complete understanding of the formation of facial clefts. The role of the proposed mechanisms in the formation of rare craniofacial clefts is not precisely defined. Nevertheless, the concepts of fusion and mesodermal penetration enable a better understanding of the problems of unusual craniofacial clefts.

CLEFTS OF THE MIDLINE CRANIOFACIAL STRUCTURES

In 1976, Tessier[22] presented a classification of craniofacial clefts. The Tessier classification has several unique features of merit. It is based on the extensive personal experience and observations of one investigator rather than on a collection of examples pulled from a review of the literature or hospital records. Therefore, the terminology and quality of observations remain uniform. In addition, the classification successfully integrates the clinical examination findings with direct observations of the underlying skeletal deformity at the time of reconstructive surgery. From the standpoint of applicability to treatment, the correlation of the clinical appearance with the surgical anatomic findings increases the value of the classification for the practicing surgeon.[12]

The simplest example of a midline facial cleft is a midline notch in the upper lip. As the notch is more complete, a median cleft of the upper lip might be expressed. This lip irregularity can be explained as an imperfect union of the paired processes. Increased disruption of the processes could lead to the formation of a bifid frenulum, a midline notch of the alveolus, a midline cleft of the palate, or a bifid nose.[12] Baibak and Bromberg[23] outlined ten cases that covered a spectrum of midline defects that included the unobtrusive upper lip midline notching, subcutaneous midline cleft lip, midline cleft lip and palate, midline cleft lip and absent premaxilla, absent septum and bridge of the nose, bifid nose, cleft nose, frontal midline encephalocele, and the objectionably severe bifid nose and midline cleft lip.

Frontonasal dysplasia and a median frontal encephalocele with orbital hypertelorism are examples of major midline developmental failures. Disfigurement of this magnitude occurs when the frontonasal prominence remains in its embryonic location.[24] The forebrain thus retains its low overlying position and interferes with the normal converging movement of the optic placodes toward the midline. Hence, the eyes remain passive in their lateralized embryonic setting while there is still active growth in the forebrain.

The host of low-frequency anomalies noted in FNM may be explained as a single malformation. If the nasal capsule fails to develop properly, the primitive brain vesicle fills the space normally occupied by the capsule, thus producing anterior cranium bifidum occultum, an arrest in the positioning of the eyes, and a lack of formation of the nasal tip.[25,26] The widow's peak hairline is a result of

the ocular hypertelorism. The two fields of hair are further apart than usual, so the fields fail to overlap sufficiently high on the forehead, thus resulting in widow's peak formation.[27]

ETIOLOGY

Although knowledge of the morphogenesis of rare facial clefts remains incomplete, an even greater void exists in the understanding of the causal agents that produce such morphokinetic disturbances. To be born "normal," the newborn must successfully overcome the possible obstacles associated with unfavorable heredity and hostile intrauterine environment. Heredity appears to play a minor role in the formation of most rare craniofacial clefts, aside from the Treacher Collins[28] and the Goldenhar syndromes.[29] In 1965, Fogh-Andersen[30] suggested that the majority of atypical clefts occur sporadically. However, in 1981, Reich et al.[31] studied the detailed family histories of patients with frontonasal dysplasia. They suggested that there is a heterogeneous pathogenesis and that heredity contributes to its cause more frequently than has previously been appreciated.

Accumulating evidence from animal and clinical studies supports a multifactorial concept of multiple interacting etiologic factors. The complexity of the problem is underlined by the vast number of teratogenic agents known to produce facial clefts. The study of nonhuman embryos and human statistics has yielded valuable information, but large voids remain in the knowledge of the pathogenesis of rare facial clefts. From investigations by Wilson[32,33],

four major categories of environmental factors have been identified: (1) radiation, (2) infection, (3) maternal metabolic imbalance, and (4) drugs and chemicals, such as anticonvulsants, antimetabolic and alkylating agents, steroids, tranquilizers, and other agents.

Midline cleft experimental models have been produced by these various teratogenic agents in animals. Burk and Sadler[34] concluded that increased facial width and/or cell death in the frontonasal process midline mesenchyme and in the neural epithelium were underlying factors in the formation of diazo-oxo-norleucine-induced median cleft face in mice. Darab et al.[35] implicated damage to the blood vessels in the frontonasal process (dilated and congested blood vessels) and to distention of the developing brain in methotrexate-induced median cleft face in mice.

In light of this knowledge of the potential harmful effects of teratogenic agents, it can be appreciated that the intrauterine environment might not be as secure and comforting for the embryo as some like to believe. The major part of the face is developed when the mother could be unknowingly pregnant. The embryo might be able to elude the teratogenic effects of a single agent only to have the balance tipped against it by a combination of drugs. Those embryos subject to detrimental genetic factors face an additional handicap.

Although most cases of FNM are sporadic and appear as an isolated incident[3,5], FNM will occasionally exhibit familial aggregation and occur as a genetic predisposition. There are reports of FNM in the literature that cite sporadic instances of FNM, however there are few familial cases reported in the literature. Gorlin[1] notes that there are several case reports[36-40] that do not represent examples of FNM.

Warkany and colleagues[41] reported in 1973 what appears to be the first familial case of FNM in two half sisters. Neither the mother nor the respective fathers had similar malformations. There was an older son by the mother who was unaffected, as well as unaffected children from each father by a previous wife. The mother's radiographic appearance did not show any minor manifestations of FNM and her karyotype was within normal limits. The two females also had bilateral polydactyly of halluces. The same facies may be observed with large anterior encephalocele, hamartoma, frontal lipoma, frontal teratoma, and intracranial cysts.[42] In 1959, Kitlowski[43] reported a similar case in which a cyst arising from the pharynx created a deformity of the nose and face. It was suggested that there was embryonic failure of development about 16 to 18 days after fertilization of the ovum. Chen et al.[44] described another similar facies in a patient diagnosed with dup(2q) syndrome and FNM.

MORPHOPATHOGENESIS

Several pathways exist through which the various causal elements can exert their detrimental forces. Interference with cell formation, cell replication, or cell migration by the etiologic agent could produce rare craniofacial clefts.

In 1970, Sedano et al.[3] reported that by employing a careful analysis of facies classification of reported cases in the literature, there appears to be no genetic basis for FNM. It was suggested that the probable cause is an interference with the normal embryological

development of the face, in particular, the nose. The timing of this interference can produce a different and particular type of facies. They further contended that FNM is clearly heterogeneous both etiologically and pathogenetically. In FNM, the nasal placodes do not develop properly, the nasal capsule is not formed, and the eyes cannot reach the midline because of persistence of the frontonasal process in its initial embryonic position.[11] As a result, the altered growth affects the development of the frontal bones and leads to the formation of cranium bifidum occultum. The result is an extremely broad face and marked hypertelorism. Smith and Cohen[27] described the related pathogenesis of the widow's peak scalp-hair anomaly that is often seen in patients with FNM. This can occur because the periorbital fields of hair growth suppression are smaller than usual and because they are widely spaced. As eyes are more normally spaced together, the fields of suppression are closer so that there is a generous overlap of the circular area of diminished hair. The further apart the fields are, as in hypertelorism, the less overlap of the area, resulting in hair growth in an inverted triangular fashion.

Pathogenesis of FNM may also be the result of frontal encephalocele, frontal lipoma, frontal teratoma, intrinsic nasal capsule abnormality, early ossification of the lesser sphenoid wings, and craniosynostosis.[9] Syndromes already identified are craniofrontonasal dysplasia, ophthalmofrontonasal dysplasia, and Greig cephalpolysyndactyly. The distribution spectrum of FNM suggests that there are subpopulations of patients with separate disorders. Therefore, Gorlin et al.[1] have proposed that there is a nonspecific group that needs further delineation.

FNM SUBGROUPS AND GENETIC CONSIDERATIONS

Toriello[45] described a distinct subgroup associated with the severe (type D) form of FNM; the description of this FNM form will be discussed in the next section. This syndrome included epibulbar dermoids, agenesis of the corpus callosum, Dandy-Walker malformation, tibial aplasia, and bilateral polydactyly of the halluces. This combination, in part or in full, has been reported by many authors.[3,38,46-50] Warkany et al.[41] reported two half-sisters with this combination; parental consanguinity had been reported.[51] In addition to this distinct syndrome that has epibulbar dermoids as a feature, the combination of oculoauriculovertebral spectrum may also occur with ocular hypertelorism and epibulbar dermoids (OFND).[29,38,52-55] When flattened encephalocele occurs, the patient appears to have FNM together with ear tags, other ear anomalies, and epibulbar dermoids. Because encephalocele occurs more commonly in the occipital region than in the frontal region, Gorlin et al.[1] suggest that such cases represent oculo-auriculo-vertebral spectrum with the encephalocele expressed anteriorly.

Sedano et al.[3] notes that the number of instances of twinning is greater in families with FNM than in the general population. Keusch et al.[56] report 2 families with twins diagnosed with FNM. There is thus far no explanation for this phenomenon. Some clinicians have maintained that FNM represents an incomplete form of twinning,

according to Gorlin.[1] Twinning of the head results from anterior duplication of the notochord. Doubling of the hypophysis constitutes the mildest form of anterior duplication. In diprosopia, a more extensive duplication, there may be doubling of the hypophysis, mouth, and nose. Doubling may lead to formation of lateral eyes and a single median eye. To this date, there is no solid evidence of duplication of any structure in FNM.[1] Although Hori[57] described the presence of two hypophyses, this case may actually have been an example of facial duplication.

CLINICAL DESCRIPTION OF FNM

FNM is generally diagnosed at birth, but there is a case that precedes this generalization. A most interesting finding was reported by Chervenak et al.[58] in which they diagnosed median cleft face syndrome by sonographic demonstration of cleft lip and hypertelorism in a 31 week fetus. FNM case reports are abundant in the foreign literature[59-64] as well as the English literature, but it was DeMyer[5] who first classified the clinical variability of frontonasal dysplasia by the presence of true ocular hypertelorism and median facial malformations. These classifications were later modified by Sedano and colleagues.[3] Anterior cranium bifidum occultum can be present in all four types of facies, and these types are described as follows. Facies A is described as ocular hypertelorism, broad nasal roots, median nasal roots, median nasal groove with absence of the nasal tip; true clefting of the midline is not present. Facies B is seen as

ocular hypertelorism, broad nasal root, deep median facial groove or true clefting affecting the nose or both the nose and the upper lip. The palate may also cleft. Facies C is summarized as ocular hypertelorism, broad nasal root, uni- or bilateral notching of the ala nasi. Facies D is a combination of facies B and C. Additionally, cleft lip and/or palate is associated with two of these facies, B and D. Thus, the facies are graded from mild (type A) to severe (type D).

Concerning the orbital region, hypertelorism, or primary telecanthus, is a constant feature. Secondary telecanthus may be seen in severe examples. Epibulbar dermoids have been noted by Cohen[8] and Edwards et al.[46] Rare findings include congenital cataracts[3], upper eyelid colobomatas[27,38,48,65], and symblepharon.[65] Iris colobomata have been recorded in a number of instances.[65] Temple et al.[66] reported four children with iris colobomatas and mental retardation, suggesting that those with FNM and coloboma of the iris might be at increased risk for mental deficiency.

The nose and ears are often affected structures. The nasal region is flattened with wide spaced nostrils and has a broad nasal root in severely affected patients. Less severe cases may show clefting or notching of the nose or nasal alae. If notching is bilateral, the nose may look square. Nose tags have been reported[6], as well as preauricular tags[58], low-set ears, absent tragus, and conductive hearing loss.[3,67]

The central nervous system is occasionally influenced in FNM affected individuals; mental deficiency may result.[46,48,68,69] As DeMyer[5] suggests, when the hypertelorism is severe, the extracephalic anomalies are more prevalent, and mental deficiency

also increases. If there are no extracephalic anomalies and the hypertelorism is mild, the probability of mental deficiency is low.[1]

Radiographically, Jaouen et al.[70] may have been the first to describe anterior cranium bifidum in 1984. Other radiographic findings are hypoplastic frontal sinuses[71-73] and the absence of the corpus callosum[5,38,48,70,72], but these may represent examples of the severe form (type D) of FNM syndrome described by Toriello.[45] About 50 percent of those with more severe facies B-D, on magnetic resonance and computer tomography examination, have dense calcification of the falx and interhemispheric lipoma.[54,74] Interhemispheric lipoma is sometimes mistaken for callosal agenesis.[55] Hydrocephaly[3,73], occipital encephalocele[49], early occlusive anterior and middle cerebral artery disease[1], as well as mild holoprosencephaly[75] have been documented in the literature.

Preaxial polysyndactyly with or without tibial hypoplasia is associated only with the severe (type D) form of FNM. Several examples of this combination have been reported.[3,41,46,47,51] Consanguinity has been noted.[51] Preaxial polydactyly alone has been found with the severe (Type D) form.[41,49] Clinodactyly[5,68,69], brachdactyly[1], parietal foramina[49], micropenis[48], cryptorchidism[1,3,5], Poland anomaly[66,76], intrauterine growth retardation[77], congenital heart anomalies[37,77,78], and choanal atresia[77] have been documented with FNM.

Oral findings include median cleft of the upper lip, especially in the more severe Type D.[3] Rarely, cleft lip and/or palate is observed as part of FNM.[57]

DIFFERENTIAL DIAGNOSIS

As with any clinical pathology, a careful and complete diagnosis of the condition must be made. A thorough differential diagnosis should be considered for each patient to rule out conditions with similar features and/or syndromes. Only then can an accurate diagnosis of FNM be made with the best judgment of the clinician.

Craniofrontonasal Dysplasia

Craniofrontonasal dysplasia, CFND, is a related entity to FNM and has been suggested to be a subpopulation of FNM. In 1979, Cohen[8] described this heritable condition in subpopulation of frontonasal dysplasia patients. He described a pedigree of a 14-year-old female proband and her affected mother, the latter affected to a much milder degree. These two were the only affecteds in this family. A male sibling was stillborn and there was no information available on any abnormalities; the mother had six spontaneous abortions. The proband's father had cerebral palsy and her maternal grandfather was 39 years old at the time of her mother's conception. It was suggested that a dominant mutation may have arisen in the maternal grandfather's primordial germ cell line. Again, no male-to-male transmission was observed, so X-linked inheritance cannot be ruled out at the present time. Kumar et al.[79] described the face of three females in a family with craniofrontonasal dysplasia, and a fourth member, male, died. They suggested that X-linked dominance with

lethality cannot be involved at this time since there is a heritable fragile 12q13 site segregating in the family separately from the gene for the CFND.

CFND has dominant inheritance[80] and seems to occur mostly in females as reported by Young[81] and confirmed by Hurst and Baraitser.[82] This entity is observed occasionally in males;[83] Grutzner and Gorlin[84] noted that females are more severely affected than males. Grutzner and Gorlin[84] looked at the phenotype and pattern of inheritance of CFND of 66 affected people in 18 families. Their findings suggest that females are severely affected, such that females had hypertelorism, broad nasal root, frontal bossing, craniosynostosis, syndactyly of the fingers and toes, and vertical grooving of the nails. The males, in contrast, had an increased bony interorbital distance, intercanthal distance between the eyes, broad nasal root, broad halluces, and vertical grooving of the nails; males had no craniosynostosis. The males transmitted the condition to only their daughters, but to none of their sons. The affected females passed the condition to about half of their daughters and half of their sons. This pattern is compatible with X-linked dominant inheritance, but the milder manifestation of the syndrome in males cannot be explained by simple mendelian genetics. Kere et al.[85] reports a family with CFND covering three generations with variable expression shown in two sisters and a father. They suggest that the expression of the gene is modified by the sex of the patient.

CFND is characterized by frontonasal dysplasia, various limb abnormalities, and premature sutural craniosynostosis. The craniofacial features of this entity include brachycephaly, asymmetric

coronal synostosis, frontal bossing, ocular hypertelorism, broad nasal bridge, hypoplastic nasal bone, bifid nose, sloping shoulders, and longitudinally grooved nails. Other reported findings are mild soft tissue syndactyly, clinodactyly of the fifth fingers, hyperextensible joints, genu valgum, thoracolumbar scoliosis, asymmetric sacrum and pubic bones, relatively small iliac bones, malocclusion, ear anomalies, broad toes, minor vertebral anomalies, skeletal defects, abnormal dermatoglyphics, and developmental delay.[11,86,87] Edwards and colleagues[46] describe their Case 2 as having ocular hypertelorism, craniosynostosis, widow's peak, cleft lip and palate. This would suggest CFND, although there are no illustrations to confirm the written description. Kumar et al.[79] and Pruzansky et al.[88] have reported clinical cases of CFND with familial transmission of the trait. Reynolds et al.[89] reported a three generation family with five affected members. An affected mother had one son and two daughters; all of whom were affected, as well as the son's only daughter. The degree of frontonasal dysplasia and craniosynostosis was more severe for the females. They suggest that this family and others represent a subpopulation of patients with frontonasal dysplasia who are at high risk for recurrence.

In 1982, Fragoso et al.[40] reported a patient who, in addition to FNM, exhibited fusion of the second and third cervical vertebrae and had pedal postaxial polydactyly. It was labeled FNM in combination with Klippel-Feil anomaly. A year later, Ishikiriyama and Niikawa[90] reported another case with the same association. The Fragoso et al.[40] patient was female and may represent an example of CFND, although craniosynostosis was not mentioned specifically. In 1950,

Webster and Deming[68] reported a case that concerned a girl with bilateral pectoral muscle hypoplasia, hypertelorism, broad nasal base with a bifid tip, neck webbing, and mild bilateral syndactyly, and coronal synostosis. It has been hypothesized by Reardon et al.[76] that this case is another reported case of craniofrontonasal dysplasia, and they support their claim with another case very similar to the case cited in Webster and Deming. Although there is a considerable amount of literature reported about CFND, there is little written about the treatment of it.[91]

Brachycephalofrontonasal Dysplasia

Teebi[92] described another syndrome having some resemblance to craniofrontonasal dysplasia, but without a bifid nose, craniosynostosis, pterygium colli, rounded sloping shoulders, or nail abnormalities. Some of these patients had shawl scrotum. This may be the same disorder as that described by Morris et al.[93] as their two male patients also had shawl scrotum. This syndrome has been termed brachycephalofrontonasal dysplasia.[94] Recently, Stratton[94] noted this syndrome in 6 individuals, 2 male and 4 female, in 4 generations, with male to male transmission.

Ophthalmofrontonasal Dysplasia

Ophthalmofrontonasal dysplasia, OFND, is basically a combination of FNM and oculoauriculovertebral anomaly.[95] The term

itself was first coined by Day[96] when a subpopulation of patients with severe eye anomalies and FNM was described. The eye abnormalities ranged from microphthalmia to anophthalmia with associated lid coloboma and conjunctival lipodermoids. Other findings included wide cleft of the ala nasi, palatal clefts, oblique facial clefts with preauricular tags, and mental retardation.[96] There have been several cases of patients affected with OFND associated with Goldenhar syndrome.[29,52] Gupta and colleagues[53] describe a similar case of a 4 month male presenting with epibulbar dermoids, malformed tragus, auricular tubercles, internal hydrocephalus, malformed nostril, and meningo-encephalocele. This was another example of the oculoauricular cranial dysplasia, as it was called at the time, associated with Goldenhar syndrome.

Greig Cephalopolysyndactyly Syndrome

Other various conditions distinguished from FNM, such as autosomal dominant Greig cephalopolysyndactyly syndrome, should be excluded by a differential diagnosis. As an example, in 1983, Kwee and Lindhout[37] reported a possible new autosomal dominant mutant of frontonasal dysplasia, coronal craniosynostosis, pre- and postaxial polysyndactyly and split nails, however, Gorlin et al.[1] diagnosed this entity to be Greig cephalopolysyndactyly syndrome. This syndrome is a combination of frontal bossing, scaphocephaly, hypertelorism, broad thumbs and halluces, preaxial and postaxial polydactyly of the hands and feet, and variable syndactyly of fingers

and toes. It was first described by Greig[97] in 1924. The clinical presentation is variable such that of the total reported population, 50 percent have frontal bossing, increased head circumference, and broad forehead. A broad nasal bridge is seen in 85 percent, broad thumbs 60 percent, broad halluces 40 percent, soft tissue syndactyly of variable severity of fingers 70 percent and toes 95 percent, postaxial syndactyly of the hands 65 percent and feet 10 percent, preaxial polysyndactyly 75 percent, and digit duplication 15 percent.[98]

Frontofacionasal Dysostosis

Frontofacionasal dysostosis should be considered in the differential diagnosis of FNM because of clinical similarities in facial appearance. In 1981, Gollop[99] first reported the syndrome affecting with severe fronto-facial malformations as a girl and her brother, whose parents were first cousins once removed. Another brother, parents and the grandparents were normal. This condition probably has an autosomal recessive trait that is characterized a midline defect of the face associated with midface hypoplasia, primary telecanthus, and severe malformations of the eyelids. Cranium bifidum occultum and prefrontal lipoma can also be present. Facial hypoplasia, palpebral defects, and autosomal recessive inheritance distinguish this syndrome from frontonasal dysostosis and FNM.[99]

Median Anterior Dysraphia of the Face

In 1969, Francesconi and Fortunato[100] reported twelve cases of median anterior dysraphia of the face that might be included in the differential diagnosis of FNM. The chief components of this malformation are fusion disturbances in the nose, upper lip, and lower lip; there are less frequent reports of fusion disturbances of the tongue and the anterior portion of the neck. They suggested that this results from a defective closure of the posterior median raphe and includes all malformations that can be traced to disturbances in the fusion of the median anterior or posterior raphe. Closure defects of those symmetrical median structures were revealed to be the result of morphological arrests, deviations, or incomplete developments.

Other Clinical Entities

Keith and Macomber[101] described an isolated case report of hypertelorism occurring in two sisters and a possible third sister that cannot be classified among known syndromes. Pai et al.[102] proposed still another expression of FNM when they reported the case of a male newborn with complete median cleft lip, cutaneous polyps, midline lipomas of the central nervous system, inguinal hernia, cryptorchidism, and clinodactyly of the fifth fingers.

Yet another type of frontonasal dysplasia has been proposed by Meinecke and Blunck.[54] The case report is the history of a mildly retarded male with frontonasal dysplasia, valvular aortic stenosis,

short stature, small head circumference, mild genital anomalies, and bilateral Sydney lines. These investigators suggest that the condition is similar to the three published cases of DeMoor.[78] The main difference in the cases is the type of congenital heart defect. This may reflect the clinical variability that is seen in several well known multiple congenital anomaly syndromes such as Noonan's syndrome.

Slover and Sujansky[103] described a three generation family that showed penetrance of frontonasal dysplasia with craniosynostosis in five members. The paternal grandmother transmitted the condition to one of her four sons, who then transmitted the entity to all three of his daughters. The mother of the probands had hypertelorism, but her condition did not appear to affect the clinical presentation of the entity since the grandmother was as severely affected as the daughters. The condition was suggested to be inherited as an autosomal dominant with reduced penetrance in the father. The variation in expression of the condition was similar to Pfeiffer syndrome and frontonasal dysplasia, but due to the severe hypertelorism, primary telecanthus, broad nasal root, and bifid tip, the suggested diagnosis was a new autosomal dominant syndrome of frontonasal dysplasia.

CEPHALOMETRIC ANALYSIS AND RADIOGRAPHIC STUDIES

The medical and dental literature contains numerous articles that concern cephalometric and radiographic interpretation, reliability, and validity. Cephalometric analysis is widely used for diagnosing, planning treatment, and monitoring surgical procedures and growth

changes in patients with dentofacial deformities.[104] Measurements made from head films are used for two general purposes: description and prediction.[105] Many different cephalometric analyses have been developed since B. Holly Broadbent's early studies in the 1930s.[106] A number of different LA analyses have been devised for orthodontic diagnosis and treatment planning by Coben[107], Downs[108-110], Jarabak[111], Jacobsen ("Wits")[112,113], McNamara[114], Ricketts[104,115,116], Sassouni[117,118], Steiner[119-121], Tweed[122,123], and Wylie.[124,125] There are also PA analyses devised for surgical uses[113,126,127] and orthodontic uses.[104,128-132] Each method deals with the same, or nearly the same, anatomic landmarks, but first describes and then classifies the individual patient's situation from a different point of view. From the various approaches, many reference points and measurements have been suggested, but a more integrated evaluation of the unique morphologic situation often is missing, hence the usefulness of some measurements is debatable.[133]

Midtgård et al.[134] discussed the reproducibility of cephalometric landmarks and measurement errors of profile (LA) cranial distances. They discussed that the three possible sources of measurement error are: (1) differences between two films of the same individual, (2) differences caused by the variation of the positioning of the landmarks, and (3) errors in the reading process. In 1986, Houston et al.[135] found that the greatest of these three errors arise in landmark identification. Järvinen[136] agreed and urged that only reference points that include relevant information should be used.

In 1984, Garn et al.[137] used a similar pattern profile analysis to describe the facies of Pierre Robin syndrome, cleft lip and palate, and

oto-palato-digital syndrome. The correlation coefficients, r_z, and the pattern profiles were described for each of these clinical entities.

The evaluation of craniofacial morphology is an indispensible tool in clinical practice and in research, and can be achieved with different approaches. Radiographic cephalometrics and photographic systems are the most suitable and therefore the most commonly used.[138] Not only can they provide points and landmarks for measurements, but they can also offer an analytical and complete evaluation of the unique craniofacial aspect of the person who is being investigated.

There have been many publications that have reported radiographic findings in FNM[1,3,5,38,45,48,49,54,55,70-75], but none have reported a scientific radiographic study of FNM. However, in 1982, Pruzansky and colleagues[88] reported a male parent and six female children affected with CFND; the mother and a son were "normal." The proband in this family was a four month old white female with a referral diagnosis of hypertelorism and abnormal cranium. The physical findings of the affected females in this family were quite variable. All females presented with orbital hypertelorism, broad nasal bridge, bifid nose, frontal bossing, abnormal dermatoglyphics, toe anomalies, and grooved nails; whereas, there was variable expression of coronal synostosis, irregularly spaced teeth, anterior dental crossbite, neck webbing, broad toes, partial syndactyly, and hyperextensible joints. This study measured only the bony interorbital distance (BIOD), head width, and cranial modulus (an indirect measure of neurocranial volume) from the posterior-anterior radiographs. Compared with standard normal values, the most

interesting finding was that the father's BIOD was larger than 2 standard deviations, adding evidence to the pedigree data that he was a carrier of the trait. Interestingly, the pedigree of the father's side of the family showed that one of the father's sisters had orbital hypertelorism, five other sisters and his mother all had orbital hypertelorism, whereas one additional sister and his father were unaffected. There was no male-to-male transmission found in this family. This case report is the only example in the FNM literature that describes the radiographic data of FNM.

There have been a few reports that recapitulate the typical facies of individuals with other craniofacial anomalies described by cephalometry. Recently, Sadler[139] described the face of patients with cleft lip, cleft lip and palate, and cleft palate. Litz[140] discussed facial data obtained with craniofacial morphometry in familial cases of cleft lip and/or palate. Other craniofacial anomalies that have been documented cephalometrically are Stickler syndrome[141], Down syndrome[142], Pierre Robin sequence[137], and oto-palato-digital syndrome.[137] Recently, an abstract was presented to discuss current research being conducted to describe the cephalometric pattern profile in Crouzon syndrome.[143]

The purpose of this study was to use cephalometry to describe and delineate the facial characteristics of the FNM patient. More specifically, this study (1) provides a comparison between familial cases, sporadic cases, and all FNM cases combined, (2) determines which cephalometric parameters are the best descriptors od differences between the groups, and (3) presents a morphometric

method for aiding in the diagnosis individuals with uncertain clinical status.

MATERIALS AND METHODS

EXPERIMENTAL AND CONTROL POPULATIONS

The FNM cases included in this study were obtained from the Craniofacial Anomalies Clinic at the Indiana University Medical Center, as well as the Center for Craniofacial Anomalies at the University of Illinois in Chicago. Inspection of the family histories revealed that these cases could be divided into two subgroups: familial cases that have more than one individual in the immediate family who are diagnosed with FNM, and sporadic cases that are believed to occur randomly in nature since no other individual in the family is known to have FNM. A total of 6 familial cases occurred in 2 families, and 8 sporadic cases presented in as many families. In one family, shown in Figure 1, there are 4 affected females, all sisters. In the other multiplex family, there was one female and one male, a young lady and her father, shown in Figures 2 and 3. In the eight sporadic cases, there were 4 males and 4 females, shown in Figures 4 through 11, respectively. This makes a total of 14 patients affected with FNM in 10 families. All families are Caucasian.

The "normal," or control, human cephalometric data used here came from the published cephalometric roentgen lateral (LA) normative values of Saksena[144] and posterior-anterior (PA) normative values of Saksena et al.[145] This data base was obtained from

Caucasians whose families were originally ascertained for a study of twins in the families.

The data for the LA radiographs are derived from a mixed serial-longitudinal data base of 190 individuals that were part of a larger study of growth and development in children conducted at the Philadelphia Center for Research in Child Growth between 1948 and 1968. The headplates were digitized and computer analyzed. Twenty-three landmarks and three planes were used to compute 84 linear and angular measurements. The data, tables, and graphs were subject to regression equations as the means of statistical analysis.[144]

The PA radiographs used for the data analysis were obtained from 601 patients at the Indiana University Medical Center. The study sample contained four data sources, the twin study, the normal siblings of Downs' syndrome patients, school children with excellent occlusion, and untreated Class I patients from the Department of Orthodontics files, all taken between 1953 and 1976. The headplates were similarly digitized and computer analyzed. Thirty-four landmarks and four planes were used to compute 95 linear and angular measurements. The data, tables, and graphs were subjected to regression equations as the means of statistical analysis.[145]

Another patient base was utilized as a second control population. Ten patients were randomly selected from the files of the Department of Oral Facial Development, Section of Orthodontics at the Indiana University School of Dentistry. All patients in this data base desired orthodontic treatment and are currently active patients; their LA and PA radiographs taken prior to initiation of orthodontic

appliances were utilized. Each patient is Caucasian, and there are 4 males and 6 females in this data base. This sample population was compared with the data base of Saksena and the affected patient data base for determination of statistical purposes.

The normal LA and PA cephalometric measurements with standard deviations were utilized for comparison with the sample FNM population of patients used in this study. These patient data bases were used to tabulate Z-scores, the number of standard deviations a particular measurement was from the standard mean. The published "normal" data bases were further utilized for controls as a baseline and additional statistical comparisons.

CEPHALOMETRIC RADIOGRAPHS

There have been no studies performed to quantify and characterize FNM via the anatomic radiographic measurements of LA and PA films. The affected data base for this study consisted of 58 LA and 43 PA cephalometric radiographs that had been previously collected as part of a study at Indiana University and the University of Illinois on those individuals affected with both sporadic and familial types of FNM.

The affected data base was also divided into those patient's radiographs that have not had any type of surgical evidence and those that had some type of surgical procedures as determined by radioopaque wires, plates, or screws that were seen on the headplates. There were 26 and 28 nonsurgical and surgical LA

radiographs, respectively. There were 24 PA radiographs for both nonsurgical and surgical groups.

All radiographs were taken using a standard cephalometer according to factory recommended instructions. These radiographs were then developed according to standard procedures employed by the departments of Radiology at Indiana University School of Dentistry and the University of Illinois School of Dentistry.

The relevant skeletal and dental landmarks, which have been repeatedly defined in previous studies, were located and used to trace each headplate prior to digitization. All tracings were made by the author and confirmed by an experienced observer in order to reduce identification error. To establish reliability in identification of radiographic landmarks, landmark points were recorded and reviewed with another researcher experienced in their identification. Using a viewbox with high intensity light, each cephalogram was traced by hand in order to learn landmark identification. A total of 10 LA and 16 PA cephalometric landmarks were identified and labeled. These landmarks are illustrated in Figures 12 and 13, respectively, and listed in Tables I and II, respectively.[146] The following seven bilateral points were used with PA films to determine facial widths: Zygomatic Process (ZY), Medial Orbitale (MO), Lateral Orbitale (LA), Superior Orbitale (SO), Maxilla (MX), Nasal Cavity Wall (NC), and Floor of Nasal Shelf (NS); Supradentale (SD) was also used. The following ten points were used for lateral films: Nasion (NA), Sella (S), Basion (BA), Articulare (AR), Zygomaxillary Superior (ZMS), Zygomaxillary Inferior (ZMI), Pterygomaxillary Fissure Inferior (PTM), Posterior Nasal Spine (PNS), Anterior Nasal Spine (ANS), and

Subspinale (A pt). These landmarks outlined the different areas of the face and met the following criteria: (1) landmarks are anatomic and descriptive of the specific anatomical region, but not constructed points, and (2) landmarks are descriptive of the different regions, thus obvious duplications were omitted. Only those landmarks in the upper and middle face were used because this is the embryologic region in which the changes of FNM are localized.

DATA PREPARATION

From these points, 15 LA and 14 PA linear and angular measurements, covering the major anatomic divisions of the head and face, were derived from each LA and PA radiograph, respectively. These are described and defined in Tables III and IV. From the LA radiographs, there were 5 facial height measurements (N-ANS, N-ZMS, N-ZMI, ZMS-ZMI, and S-PNS), 5 facial depth measurements (S-N, S-BA, N-BA, S-ANS, and PNS-ANS), and 5 facial angles (S-N/ZMS-ZMI, PNS-ANS/N-A, S-N-A, S-N/PNS-ANS, and N-S-BA). These are illustrated in Figures 14, 15, and 16. From the PA radiographs, there are 6 facial width measurements (MOR-MOL, LOR-LOL, NR-NCL, NSR-NSL, ZYR-ZYL, and MXR-MXL), 6 facial height measurements (MOR-NCR, MOL-NCL, NCR-NSR, NCL-NSL, NSR-MXR, and NSL-MXL), and two facial depth measurements (MXR-ZYR and MXL-ZYL). These are illustrated in Figures 17 and 18. Radiograph magnification for both Indiana and Illinois

radiographs was determined previously by another investigator and used to standardize linear measurements.

These linear and angular measurements were obtained from each individual radiograph by using a GTCO@ computer digitizer and a custom designed software package by Saksena. The program converted X and Y coordinates of each variable landmark into a series of linear and angular measurements. To some degree, intraexaminer variability was assessed by entering sets of digitized points twice and comparing measurements. The computer program detected errors of up to 1 millimeter when the points were re-entered. When such errors were detected, they were redigitized until the error was within the established tolerance.

Based upon the previously discussed findings of Midtgård et al.[134], Houston et al.[135], and Järvinen[136], only relevant landmarks were used in this study, and every effort was made to reduce possible error. Intraexaminer reliability was reduced in the LA and PA tracings through careful and complete landmark identification by the main examiner, as well as multiple digitizing of each cephalogram. Also, other examiners were utilized to test for interexaminer reliability.

Before the research project began, a careful understanding of the craniofacial structures was ascertained. A dry skull was used to identify the actual anatomic landmarks so that a more precise selection of landmarks on the radiographs could be made. Acetate drawings were done multiple times for all films in order to become better acquainted with the clinical entity of FNM. After learning this procedure, the headplates were first digitized with the acetate paper tracing in place on the radiograph while learning to use the computer

and its software program. Ultimately, each film was digitized with no acetate paper on the radiograph so that an accurate and unbiased identification of the landmarks would be made. All of this training proved to be invaluable.

Some landmarks, i.e., ANS, SO, occasionally proved to be difficult to visualize, so these points were estimated. To minimize variation, which could be due to subjective decision making as well as to inherent examiner variability, outlying points with a measurement greater than 3 standard deviations were routinely remeasured. To determine the reproducibility of measurement for intraexaminer reliability, 10 LA and 10 PA cephalograms from the FNM patient data base were randomly selected and digitized three times. To assess interexaminer reliability, these same twenty films were digitized by two experienced clinicians. One examiner was a trained orthodontist who is a section chairman in the Department of Oral Facial Development and whose practice treats many patients with craniofacial anomalies, including FNM. The other examiner is a dentist with a specialty in the dental diagnostic sciences and is currently a Ph.D. candidate working on a similar project.[143] This process would also allow an estimate of reliability of landmark identification.

Because of the differential effects of growth, it is necessary to perform a regression analysis in order to bring all subjects to a "standard age and sex." The use of a Z-score avoids this complication because it is a pure unit value representing the number of standard deviations a given measurement differs from a normal population, or zero. This was also done for the published control data.[144,145] Ideally,

for this control population, the Z -score equals zero, but this is not possible without thousands of subjects. Routinely, normal Z-scores were more than zero, but less than one standard deviation. The effect of age and sex differences within the population data was avoided by determining Z-scores for each measurement. Z-scores are calculated by determining the difference between the raw sample individual measurement for each patient from the appropriate age and sex matched control population mean, then dividing by the variable's standard deviation in the same control population. The Z-scores for both the FNM patient data base and the orthodontic patient control data base were determined from the previously published age and sex matched normal values.[144,145] There are many other samples of control populations with normal values, for example Rakosi[147] and Sassouni[148], however, the Saksena et al. LA[144] and Saksena PA[145] data base is conviently loaded on another computer with a Z-score program that can easily determine the appropriate Z-score for each measurement. All subsequent analyses and comparisons were made from the Z-score data.

STATISTICAL ANALYSIS

Statistical analysis sought to reject the null hypothesis that there are no significant differences in the mean measurements of the overall pattern of measurements Z-scores between the patients with FNM and the two control populations, both previously published and the new control population. The FNM data was divided into three

groups: familial cases, sporadic cases, and all of the cases combined. This last grouping, combined, was used to test the assumption that there is no difference between familial and sporadic cases of FNM.

First, the relationship between the control population and the published population was examined in order to provide the baseline for further comparisons. The study sample was then compared with the control population using univariate analyses. The control sample was compared with the published population using univariate analyses. Analysis of variance, ANOVA, was used to determine the difference in the means for each variable in the new control population. Student-Newman-Keuls tests were performed to determine the significance between the measurement variable in each of the three experimental groups.

The relationship between the FNM populations (familial, sporadic, surgical, nonsurgical, and combined) and the control population was examined in order to provide a comparison with previous studies. Again, ANOVA and Student-Newman-Keuls tests were utilized to determine significant differences ($p<.05$) between the Z-score measurements from each group and those of the control group. Mean pattern profile analysis, as described by Garn et al.[137,149] was used to depict the overall relationship between the sample group and published normal measurements. Garn et al.[137] suggest that all Z-scores for a single pattern profile can be used to calculate the measure "σ_z," the standard deviation of Z-scores, in order to express degree of patterned deviation from "normals." They also noted that the pattern variability index, or "r_z," is a measure of the overall similarity between two pattern profiles. This latter calculation is also

known as providing a correlation coefficient between patterns of different groups.

RESULTS

INTRAEXAMINER RELIABILITY

Appendix A presents mean Z-scores, the standard deviations or σ_z, the standard errors, and ANOVA F and P values for the LA measurements; Figure 19 shows the graphic presentation of this data with standard errors. There are no significant differences within the examiner using the mean Z-scores since the lowest P-value is 0.977 for S-N-A or S-N/PNS-ANS.

Appendix B displays mean Z-scores, the standard deviations or σ_z, the standard errors, and ANOVA F and P values for the PA measurements; Figure 20 reveals the graphic presentation of this data with standard errors. There are no significant differences within the examiner using the mean Z-scores since the lowest P-value is 0.972 for NCR-NCL.

INTEREXAMINER RELIABILITY

Appendix C presents mean Z-scores, the standard deviations or σ_z, the standard errors, and ANOVA F and P values for the LA measurements; Figure 21 shows the graphic presentation of this data with standard errors. There are no significant differences between the examiners using the mean Z-scores since the lowest P-value is 0.925 for N-ZMS.

Appendix D displays mean Z-scores, the standard deviations or σ_z, the standard errors, and ANOVA F and P values for the PA measurements; Figure 22 reveals the graphic presentation of this data with standard errors. There are no significant differences between the examiners using the mean Z-scores since the lowest P-value is 0.989 for NCR-NCL.

CONTROL POPULATION COMPARED TO PUBLISHED NORMAL VALUES

Means Z-scores, standard deviations or σ_z, and standard errors, were calculated for each of the 15 LA measurements for the control patient data base and are shown in Appendix E. The graphic presentation of this data with the standard errors is shown in Figure 23. The mean Z-scores range from -0.45 to 0.49 with a standard error range of 0.71 to 0.95 and a standard error range of 0.20 to 0.30. These values fall within one-half standard deviation from the zero baseline, and no values are significant at a level of $p<0.05$.

Means Z-scores, standard deviations or σ_z, and standard errors, were calculated for each of the 14 PA measurements for the control patient data base and are shown in Appendix F. The graphic presentation of this data with the standard errors is shown in Figure 24. The mean Z-scores range from -0.57 to 0.34 with a standard error range of 0.83 to 0.92 and a standard error range of 0.25 to 0.29. These values fall within one-half standard deviation from the zero baseline, and no values are significant at a level of $p<0.05$.

FRONTONASAL MALFORMATION PATIENTS COMPARED TO CONTROL POPULATION BY LA MEASUREMENTS

The mean Z-scores, the standard deviation (σ_z), and the standard error were calculated for each of the 15 measurements and are listed in Appendix E. Because the Z-score measurements standardize for age and sex differences within and between samples, this data formed the basis for subsequent analyses. The ANOVA and Student-Newman-Keuls tests indicated that 7 of the 15 measurements demonstrated statistically significant differences ($P<0.05$) from the control population values when the familial and sporadic subgroups were combined and considered as one. This data is shown in Figure 25. In order to organize the data, the results from the ANOVA and Student-Newman-Keuls tests were divided into separate anatomic areas of the face. This allows for a clearer comparison of the findings from the present study with those from past literature.

The mean Z-scores for two of the four middle anterior facial height measurements (N-ANS and N-ZMS) were significantly diminished compared to the control population, as well as S-PNS, a measure of the middle posterior facial height. However, anterior facial height in the zygomatic region itself (ZMS-ZMI) was significantly larger compared to the same control population; only N-ZMI was not significantly different. With respect to the facial depth, only two of the measurements, posterior cranial base and maxillary position, (S-BA and S-ANS, respectively) were significantly different from the control group. Only one facial angle, anterior cranial base to zygomaxillary

process (S-N/ZMS-ZMI), was significantly smaller than the control patient base.

The combined mean Z-score pattern profile in Figure 26 depicts the general craniofacial measurment trends in the combined, familial, and sporadic subgroups, when compared to both the published "normal" group and the control population used in this study. The correlation coefficient r_z for the combined control group comparison is $r_z = 0.378$, a low-to-moderate level of correlation.

Comparison of the Familial and Sporadic Subgroups to the Two Normal Groups

When the total sample of FNM is divided into two groups according to type of occurance, the two subgroups familial and sporadic are recocognized. These were then compared to the published controls and the control sample used in this study. ANOVA and Student-Newman-Keuls tests were again utilized to determine the significance between all measurement Z-score means and the control population at a $p<0.05$ level.

Again, middle facial height, as measured by N-ANS and N-ZMS, was significantly decreased in both the familial and sporadic subgroups. Also, middle facial height in the zygomatic region (ZMS-ZMI) was increased significantly in both subgroups, and middle posterior facial height (S-PNS) was decreased significantly in both subgroups.

Considering the facial depth, both familial and sporadic subgroups demonstated significantly decreased posterior cranial

base lengths (S-BA) and maxillary position (S-ANS). Interestingly, only the familial subgroup showed a significant decrease from the control population when looking at the effective cranial base length (N-BA). It should also be noted that the familial cases demonstrated a slight decrease in maxillary length (PNS-ANS), whereas both the sporadic and combined subgroups showed slight increases. None of these were significant, however.

For the facial angles, only the sporadic subgroup demonstrated a significant decrease from the control population like the combined group did. A similar but not significant trend was seen in the anterior-posterior position of the maxilla (S-N-A). Only the familial subgroup showed a significant difference in cranial flexure angle.

The familial and sporadic subgroups were compared to the control for their correlation coefficients. They demonstrated moderate ($r_z = 0.592$) and low ($r_z = 0.289$) correlations, respectively. This is illustrated in Figure 26.

FRONTONASAL MALFORMATION PATIENTS COMPARED TO CONTROL POPULATIONS, PA MEASUREMENTS

The mean Z-score, the standard deviation (σ_z), and the standard error were calculated for each of the 14 PA measurements and are listed in Appendix F. Again, because the Z-score measurements standardize for age and sex differences within and between samples, this data formed the basis for subsequent analyses. The ANOVA and Student-Newman-Keuls tests indicated that 5 of the 14 measurements demonstrated statistically significant

differences ($P<0.05$) from the control population values both when the familial and sporadic subgroups were combined and when considered as one. This data is shown in Figure 27. In order to organize the data, the results from the ANOVA and Student-Newman-Keuls tests at a $p<0.05$ significance level were divided into separate anatomic areas of the face. This allows for a clearer comparison of the findings from the present study with those in the literature.

The mean Z-scores for both of the interorbital facial width measurements (MOR-MOL and LOR-LOL) were significantly increased compared to the control population. However, bimaxillary width was significantly decreased when compared to the control population. With respect to the facial height, only middle facial height right and left measurements (MOR-NCR and MOL-NCL) were significantly different smaller than the control group. There were no significant differences in facial depth.

The combined mean Z-score pattern profile in Figure 28 depicts the general craniofacial trends in the combined subgroup, as well as the familial and sporadic subgroups, when compared to the published control data and to the control population used in this study. The correlation coefficient $r_z = 0.418$ suggests a low-to-moderate level of correlation.

Comparison of the Familial and Sporadic Subgroups with the Two Normal Groups

Just as in the LA FNM data base, the familial and sporadic subgroups were divided from the combined sample into two

subgroups and compared to the published controls and the control sample used in this study. ANOVA and Student-Newman-Keuls tests were again utilized to determine the significance at a $p<0.05$ level between all measurement Z-score means and the control population.

Interorbital width, in both familial and sporadic subgroups, was significantly larger than in the control population. However, looking at other facial width measurements, only the sporadic subgroup was significantly smaller in the bimaxillary width. The familial subgroup was significantly smaller than the control population, and the sporadic and combined subgroups were smaller, but not significant.

The middle facial height was significantly smaller on the right and left sides of the face in both the familial and sporadic cases when compared with the control population. All other facial height and facial depth measurements were not significantly different at a $p<0.05$ level.

The correlation coefficients between the control and the familial and sporadic subgroups are $r_z = 0.410$ and $r_z = 0.415$, respectively. This is illustrated in Figure 28. These values are representative of low-to-moderate correlation.

COMPARISONS AMONG FAMILIAL, SPORADIC, AND COMBINED SUBGROUPS

It was decided to ungroup the combined subgroup into the familial and sporadic subgroups on the assumption that there may be a genetic difference between the familial and the sporadic subgroups. With respect to the LA measurements, the familial subgroup of middle anterior facial height (N-ZMS) and cranial flexure(N-S-BA) were

significantly smaller than both the sporadic and combined subgroups. The familial subgroups of middle posterior facial height (S-PNS) and anterior cranial base to zygomaxillary process (S-N/ZMS-ZMI) were significantly larger than both the sporadic and combined subgroups. The sporadic and combined subgroups were not significantly different from each other. There were no significant differences between familial, sporadic, and combined subgroups when looking at the PA measurements.

The correlation coefficient r_z provides a measure of similarity between two pattern profiles. As seen in Figure 26, the highest correlation observed in the LA data is between the sporadic and combined groups at $r_z = 0.986$, a very high correlation. Familial compared to combined is also very high, with $r_z = 0.831$, while the relationship between familial and sporadic subgroups is lower at $r_z = 0.728$ but still demonstrates a moderately high correlation. As observed in Figure 28, the three coefficients for the PA data comparisons, familial to sporadic, familial to combined, and sporadic to combined, show high correlation values of $r_z = 0.924$, $r_z = 0.945$, and $r_z = 0.998$, respectively.

SURGICAL AND NONSURGICAL FRONTONASAL MALFORMATION PATIENTS COMPARED TO CONTROL AND COMBINED POPULATIONS, LA AND PA MEASUREMENTS

Figure 29 shows the graphic depiction of the surgical and nonsurgical LA radiographs when compared to the combined and control populations. This data is listed in Appendix I. A significant

difference towards improvement with surgery is noted between the nonsurgical and surgical groups in the measurements of middle anterior facial height (N-ANS, N-ZMS, and N-ZMI), anterior cranial base length (S-N), posterior cranial base length (S-BA), effective cranial base length (N-BA), and maxillary position (S-ANS). A significant difference away from improvement with surgery is noted between the nonsurgical and surgical groups in the measurements of middle anterior facial height (ZMS-ZMI), maxillary length (PNS-ANS), maxillary angle (PNS-ANS/N-A), and maxillary horizontal angle (S-N-A).

Figure 30 shows the graphic depiction of the surgical and nonsurgical PA radiographs when compared to the combined and control populations. This data is listed in Appendix J. A significant difference towards improvement with surgery is noted between the nonsurgical and surgical groups in the measurements of lateral orbital width (LOR-LOL), zygomatic width (ZYR-ZYL), maxillary width (MXR-MXL), nasal cavity wall to nasal shelf (only NCR-NSR), and middle facial depth (only MXR-ZYR). A significant difference away from improvement with surgery is noted between the nonsurgical and surgical groups in the measurements of nasal shelf width (NSR-NSL) and middle facial depth (only MXL-ZYL).

FIGURES AND TABLES

FIGURE 1. Beginning at upper left and rotating clockwise: Mother, case 6.1 at approximately 7 months of age, case 6.2 at approximately 1 year and 9 months of age, father, unaffected son, case 6.4 at approximately 4 years and 5 months of age, and case 6.3 at approximately 5 years and 5 months of age.

FIGURE 2. Case 10.1 at approximately 9 years and 3 months of age.

FIGURE 3. Case 10.2 at approximately 5 years and 1 month of age.

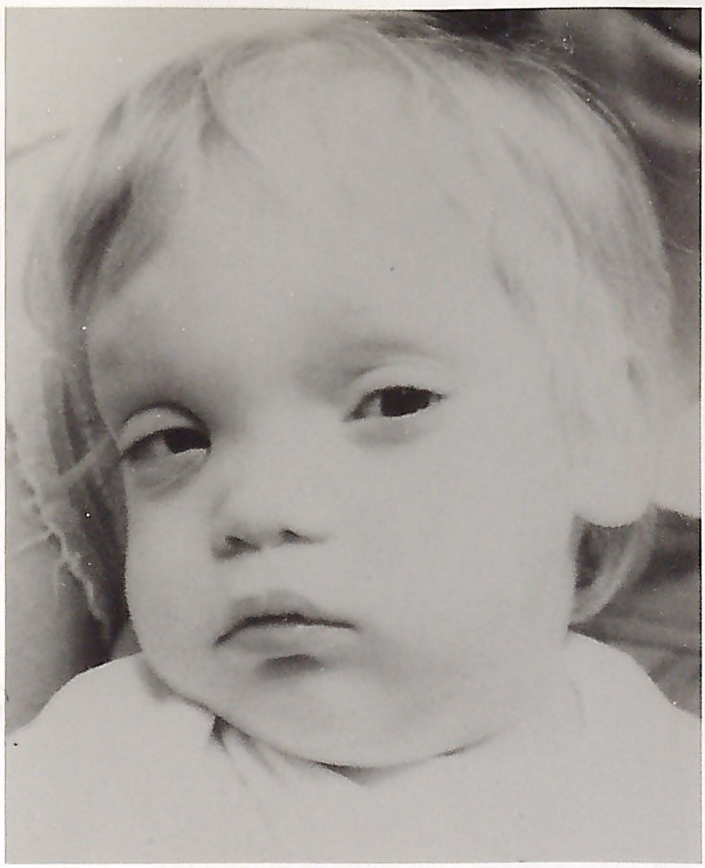

FIGURE 4. Case 1.1 at approximately 1 year and 7 months of age.

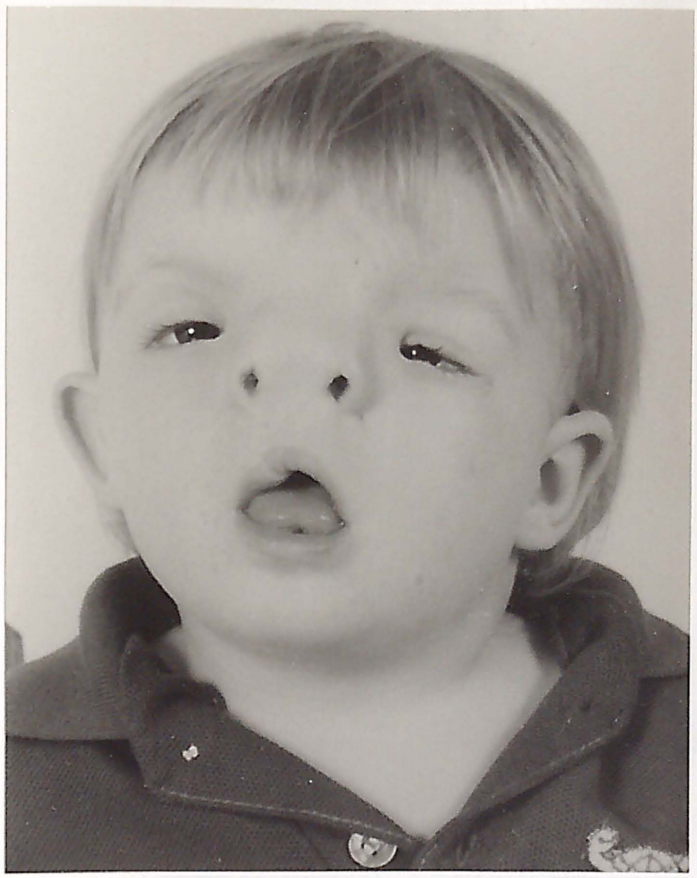

FIGURE 5. Case 5.1 at approximately 1 year and 4 months of age.

FIGURE 6. Case 7.1 at approximately 3 years and 7 months of age.

FIGURE 7. Case 9.1 at approximately 3 years and 4 months of age.

FIGURE 8. Case 2.1 at approximately 4 months of age.

FIGURE 9. Case 3.1 at approximately 15 years and 1 month of age.

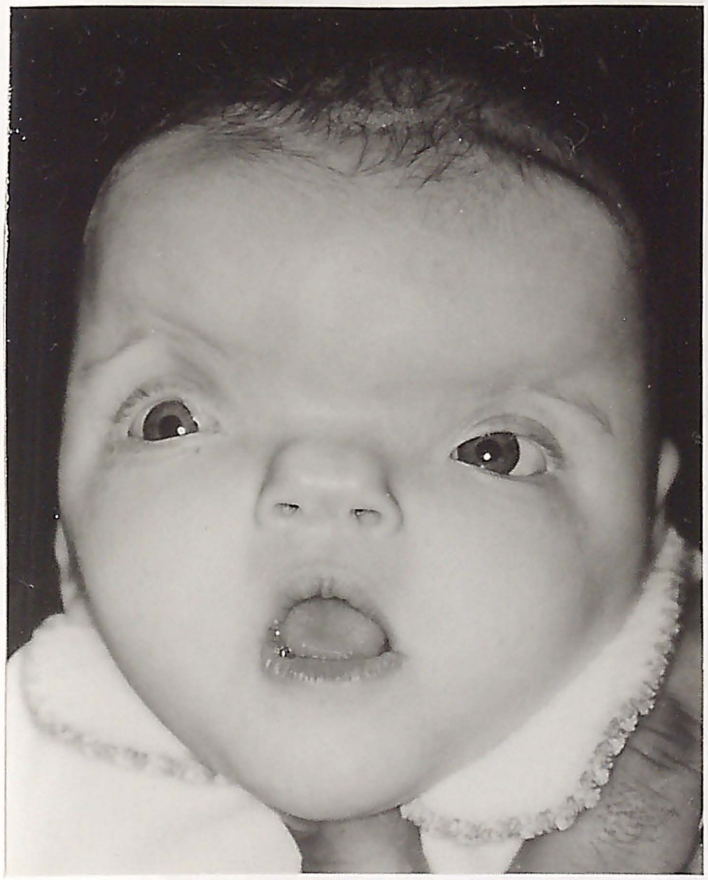

FIGURE 10. Case 4.1 at approximately 3 months of age.

FIGURE 11. Case 8.1 at approximately 18 years and 3 months of age.

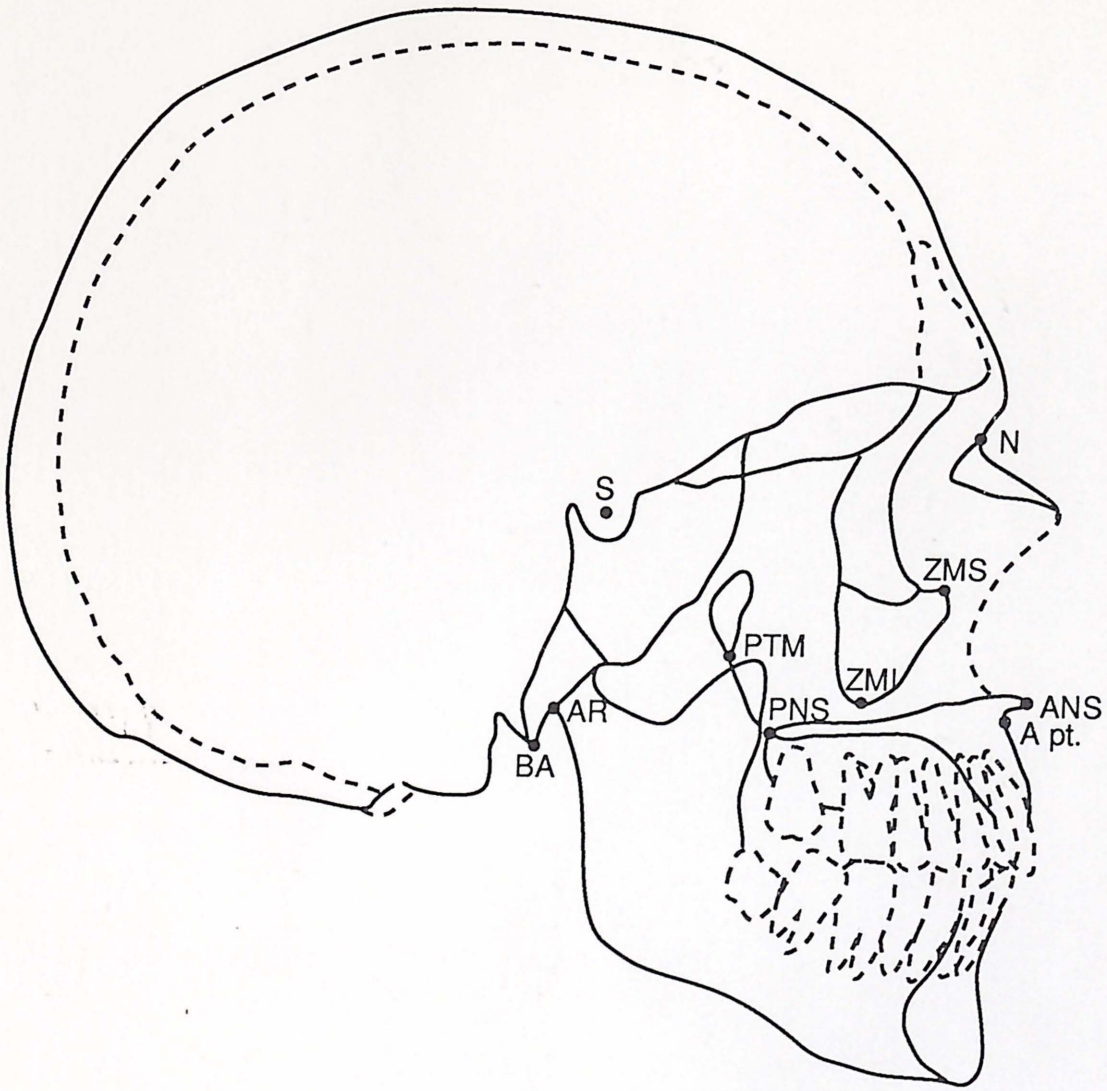

FIGURE 12. Graphic representation of the LA cephalometric landmarks utilized for all measurements.

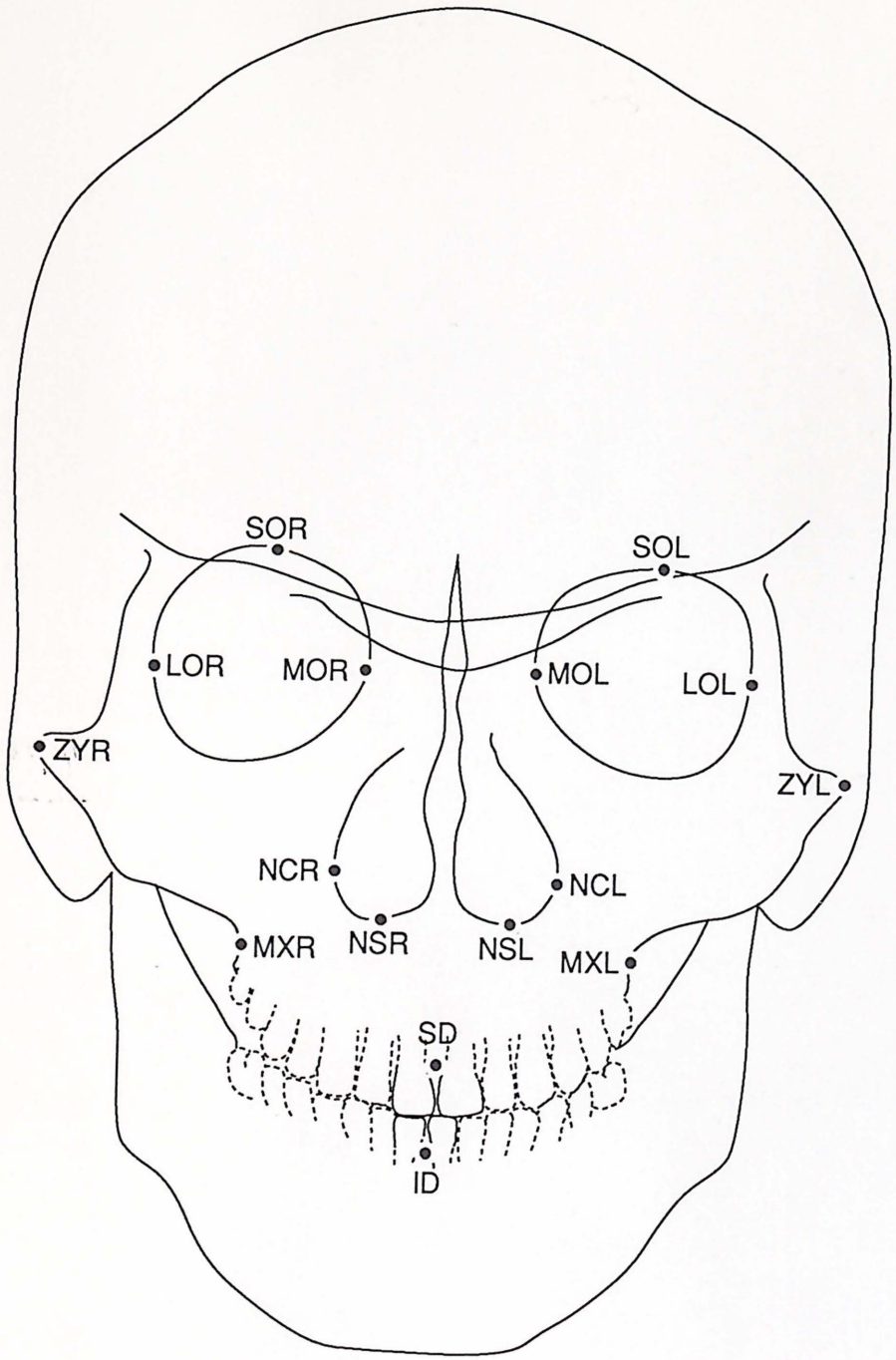

FIGURE 13. Graphic representation of the PA cephalometric landmarks utilized for all measurements.

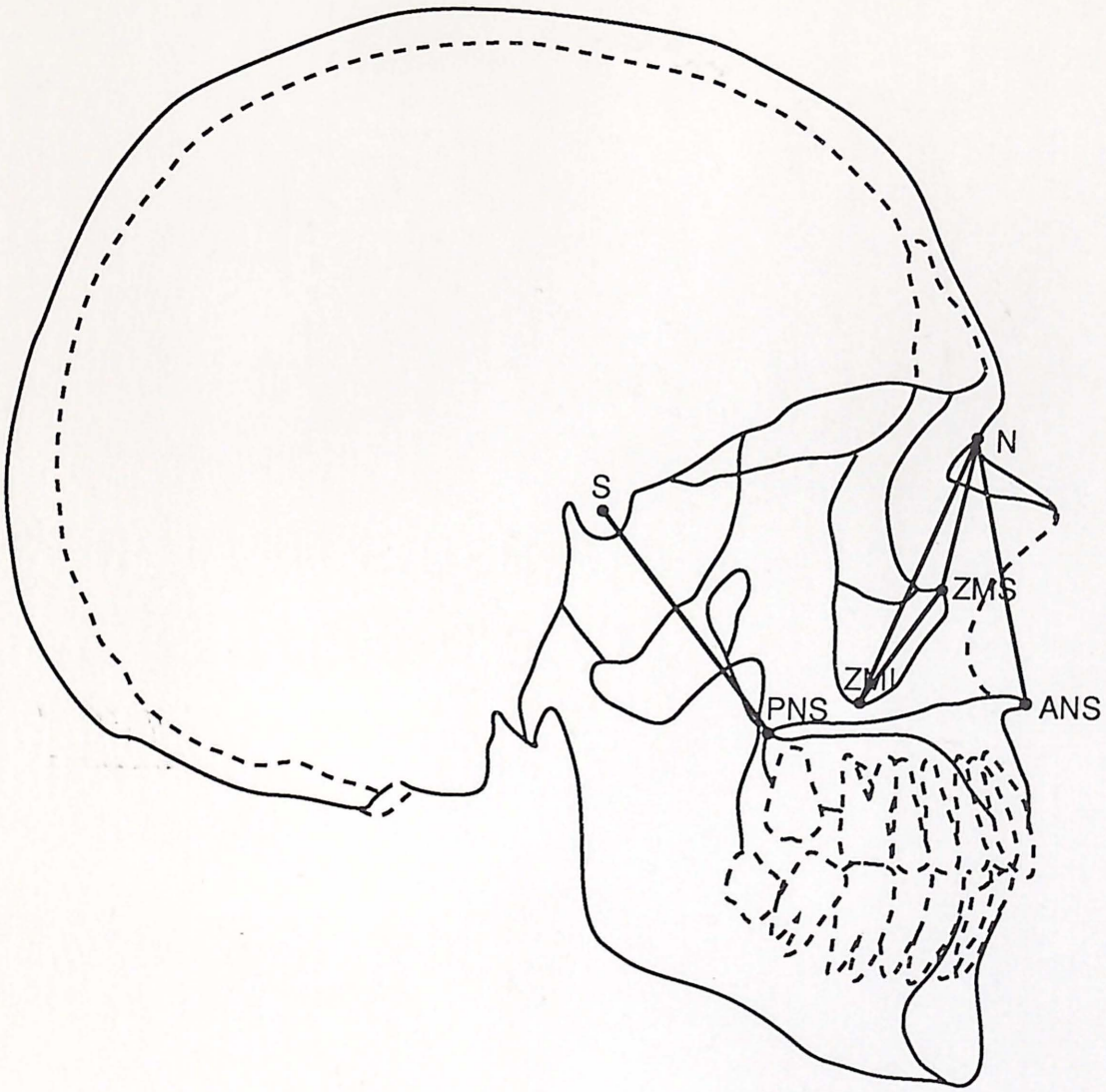

FIGURE 14. Graphic representation of the lateral cephalometric facial height measurements.

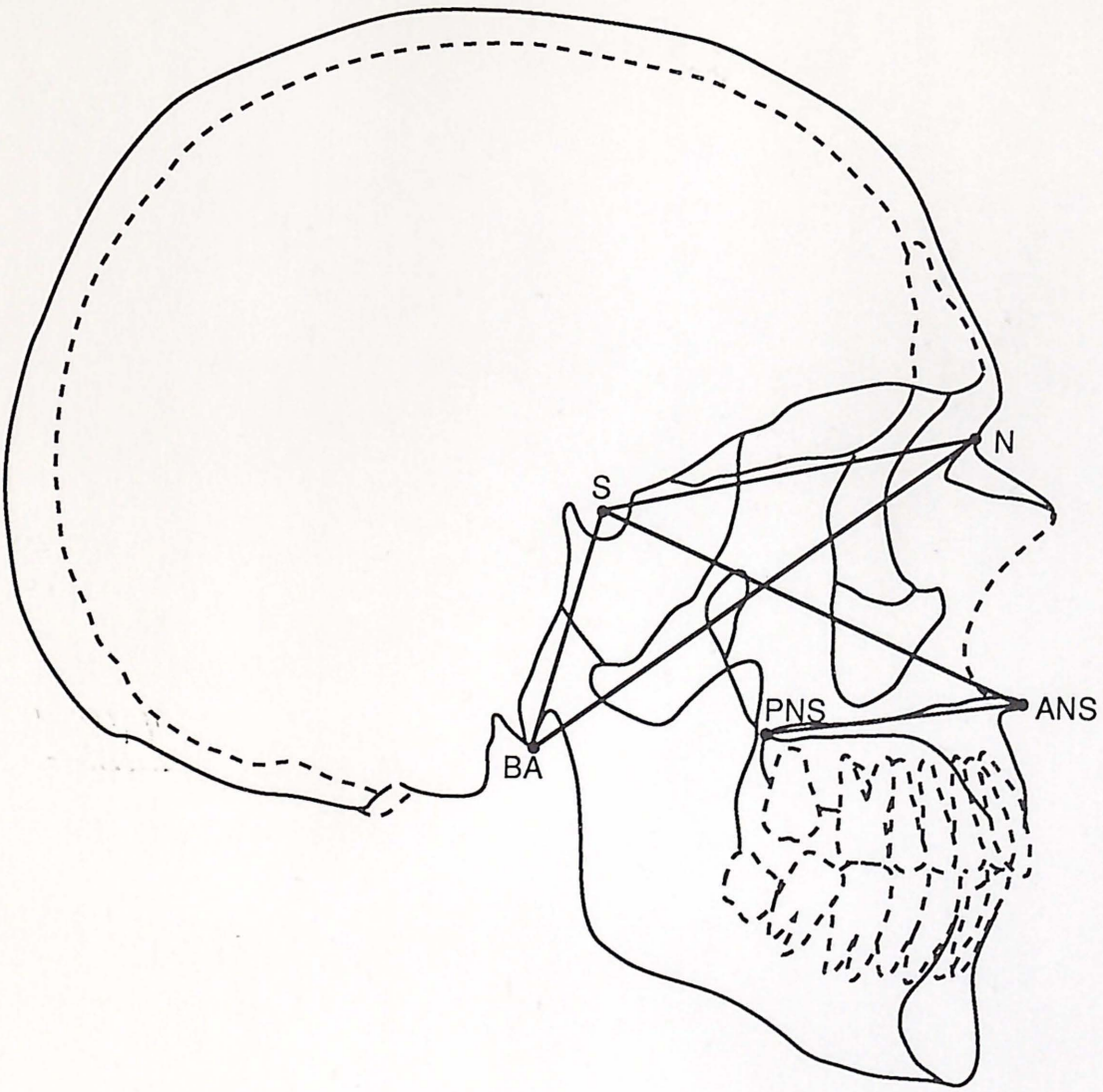

FIGURE 15. Graphic representation of the lateral cephalometric facial depth measurements.

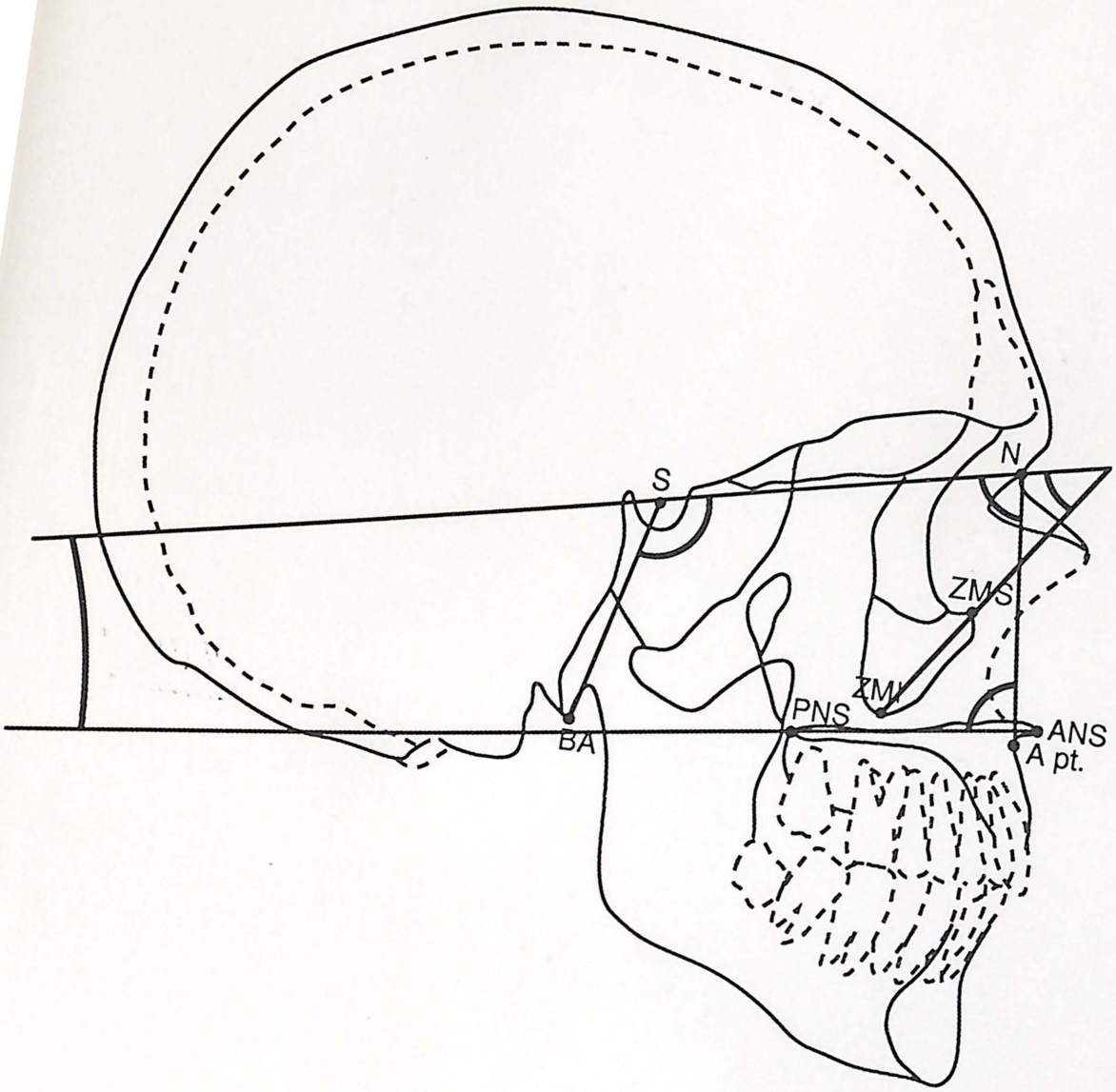

FIGURE 16. Graphic representation of the lateral cephalometric facial angular measurements.

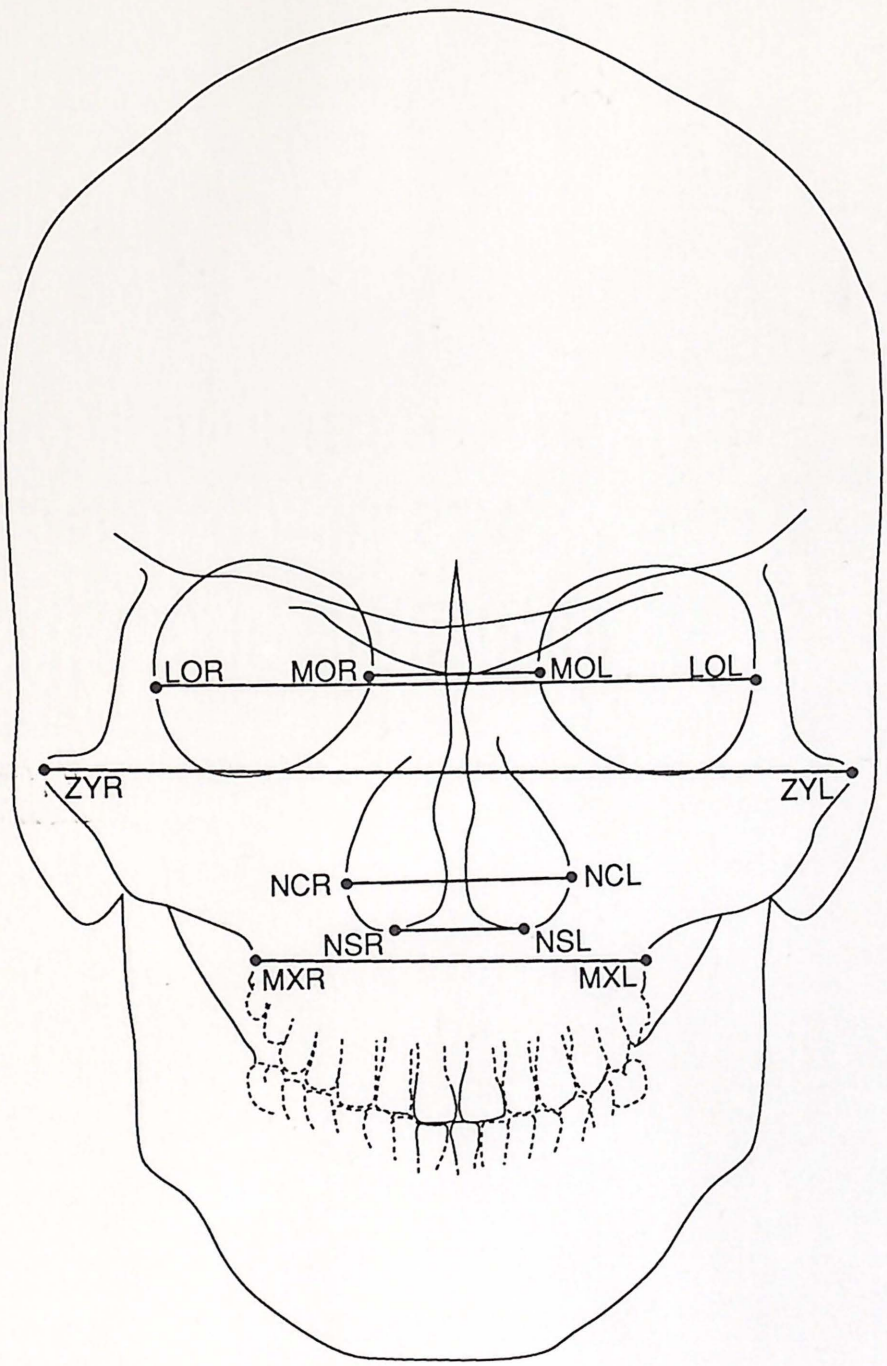

FIGURE 17. Graphic representation of the posterior-anterior cephalometric facial width measurements.

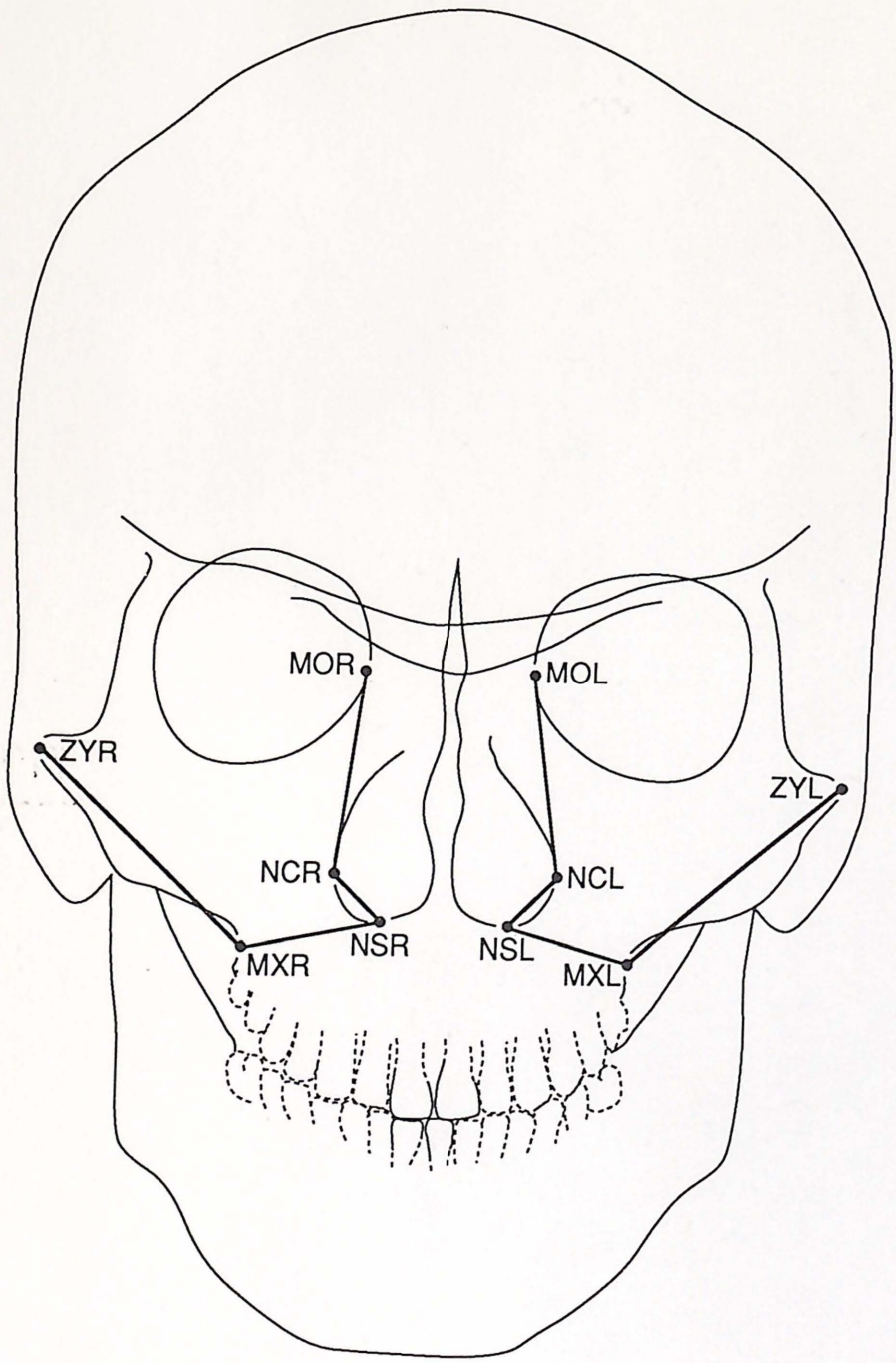

FIGURE 18. Graphic representation of the posterior-anterior cephalometric facial height and depth measurements.

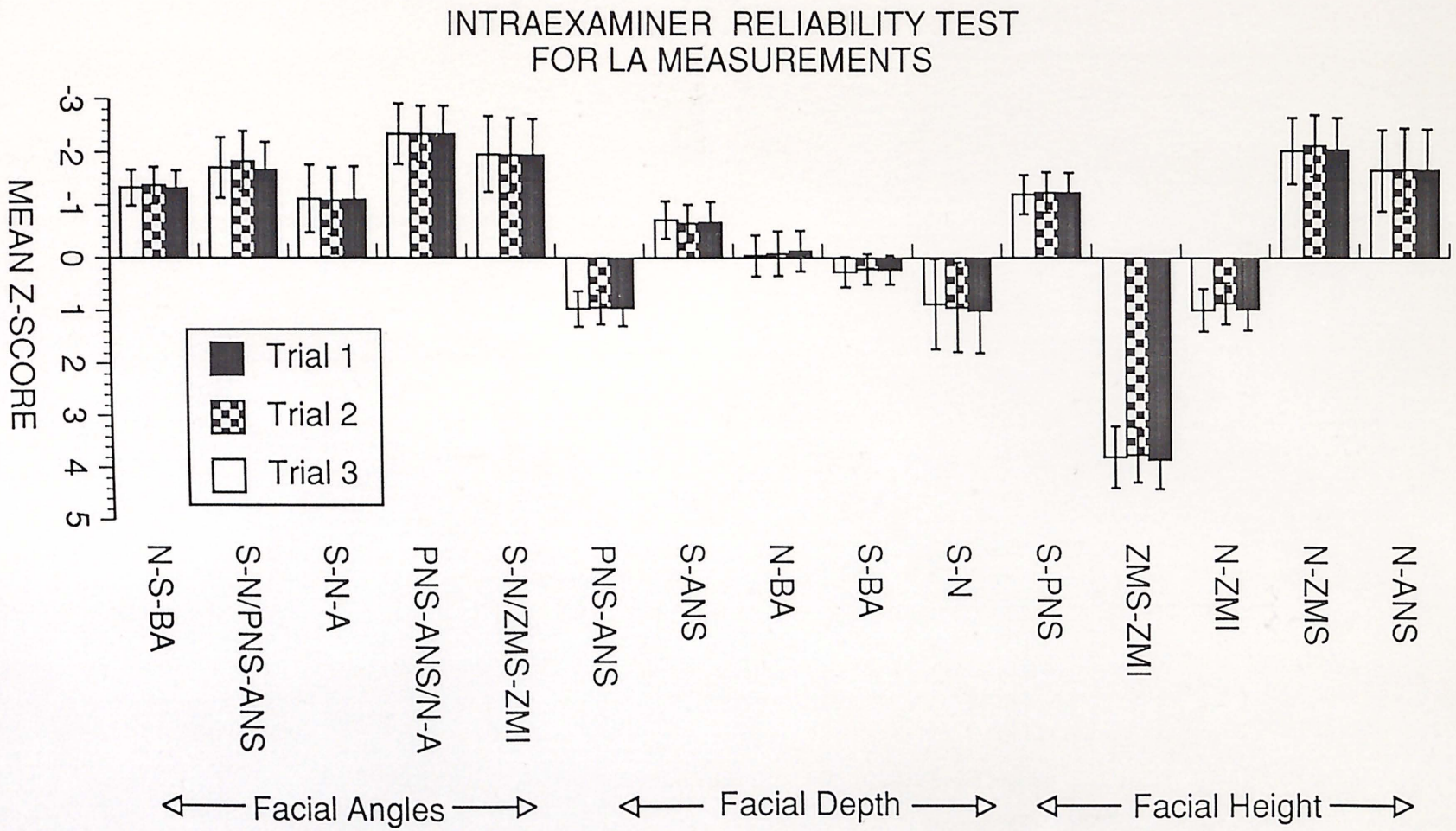

FIGURE 19. Mean Z-score pattern profiles with standard errors of 10 randomly chosen LA radiographs derived from three trials by one examiner for intraexaminer reliability. The zero baseline represents the population mean for the 15 variables as reported by Saksena et al. (1987).

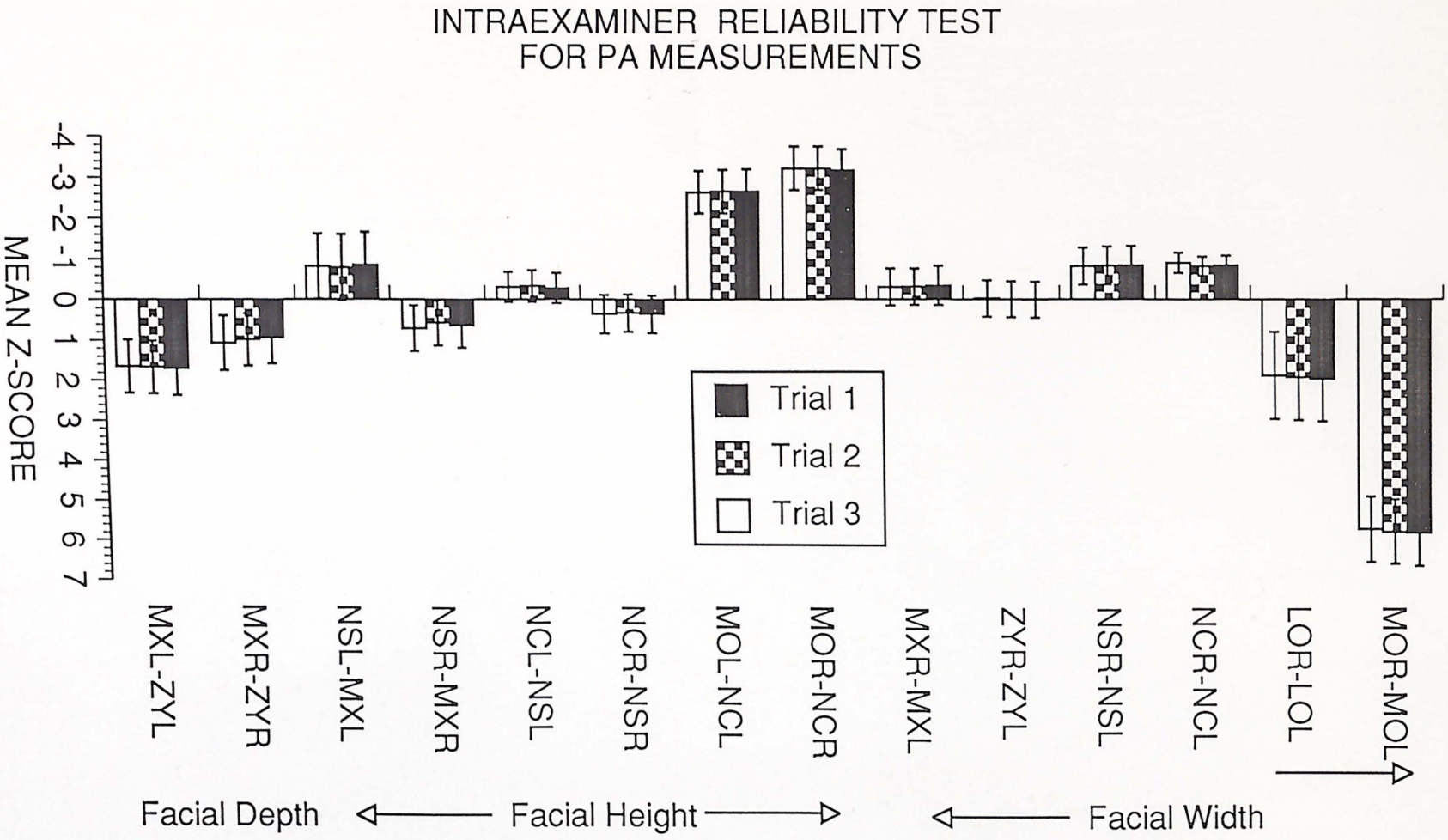

FIGURE 20. Mean Z-score pattern profiles with standard errors of 10 randomly chosen PA radiographs derived from three trials by one examiner for intraexaminer reliability. The zero baseline represents the population mean for the 14 variables as reported by Saksena (1990).

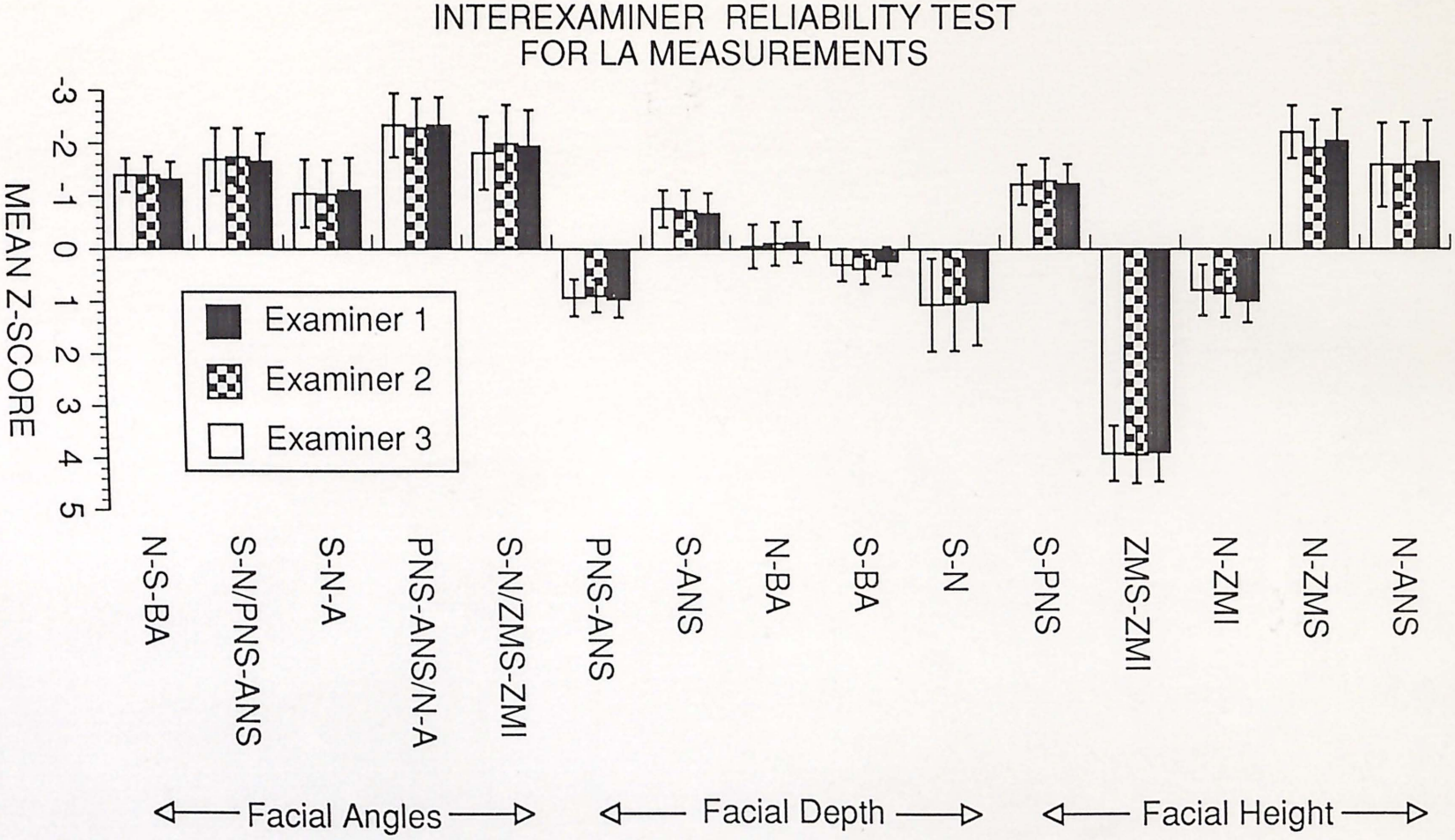

FIGURE 21. Mean Z-score pattern profiles with standard errors of 10 randomly chosen LA radiographs derived from a single trial of three examiners for interexaminer reliability. The zero baseline represents the population mean for the 15 variables as reported by Saksena et al. (1987).

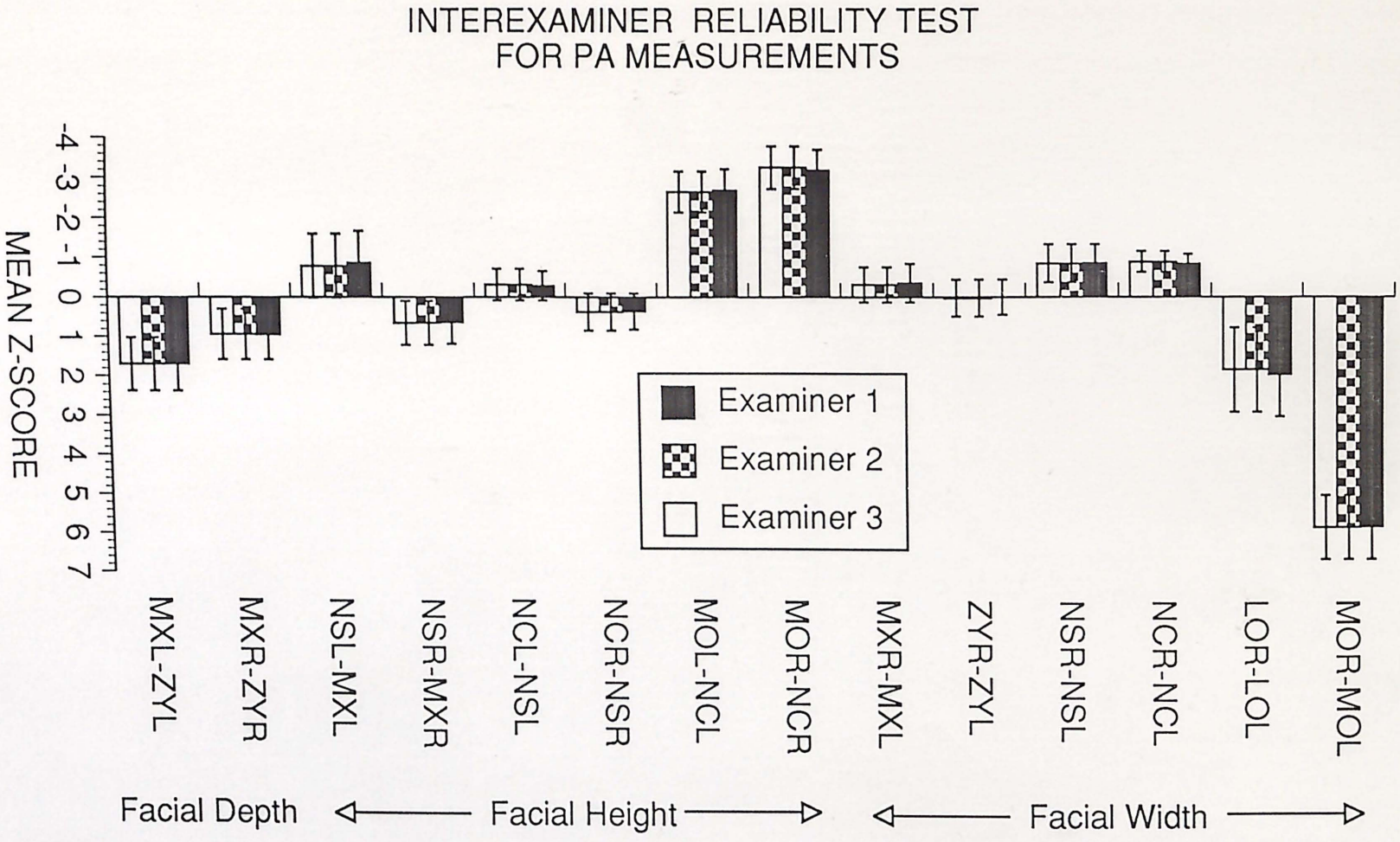

FIGURE 22. Mean Z-score pattern profiles with standard errors of 10 randomly chosen PA radiographs derived from a single trial of three examiners for interexaminer reliability. The zero baseline represents the population mean for the 14 variables as reported by Saksena (1990).

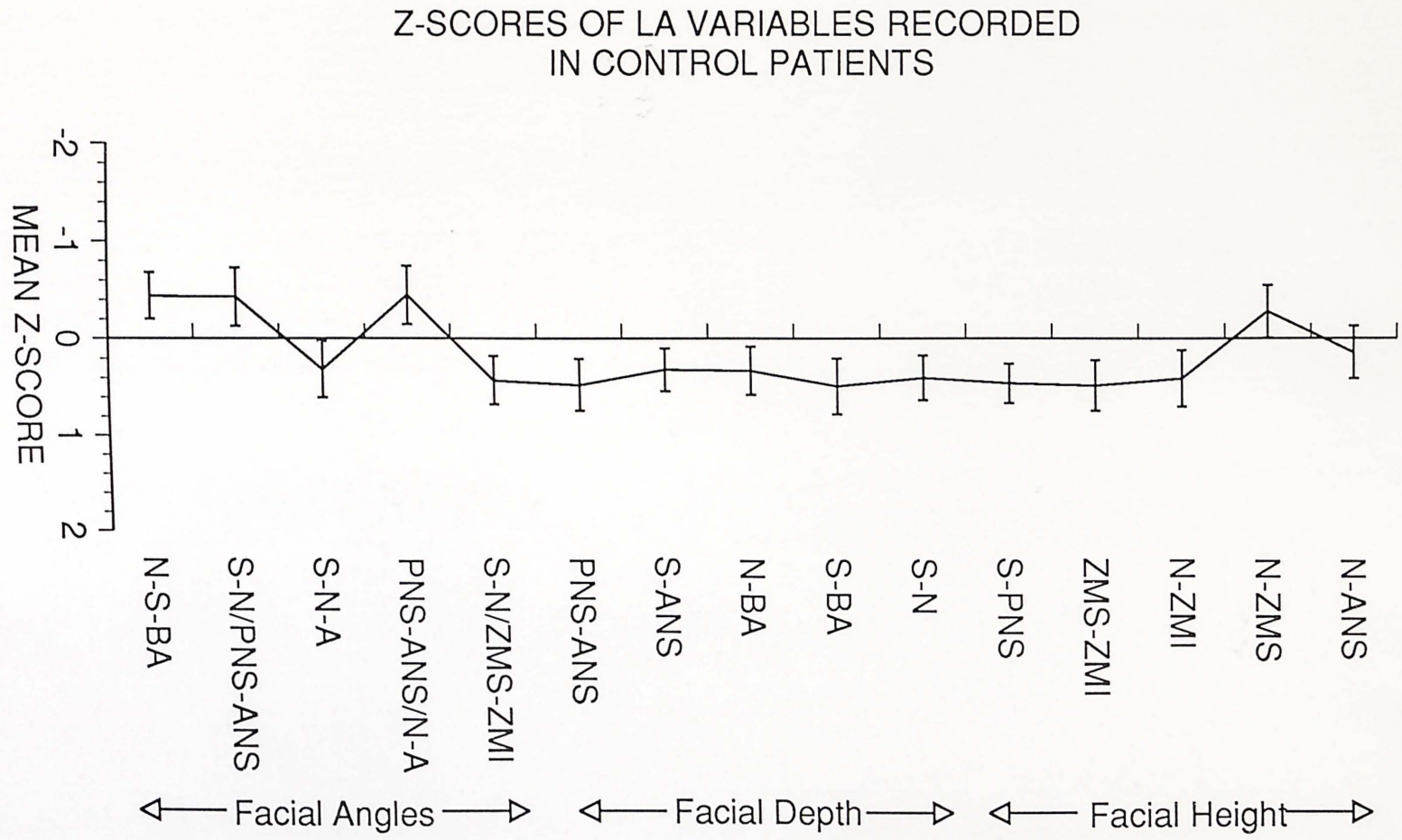

FIGURE 23. Mean Z-score pattern profile (with standard errors) of variables from LA radiographs for 10 randomly selected "normal" patients taken from an orthodontic patient file. The zero baseline represents the unaffected population mean for the 15 variables as reported by Saksena et al. (1987).

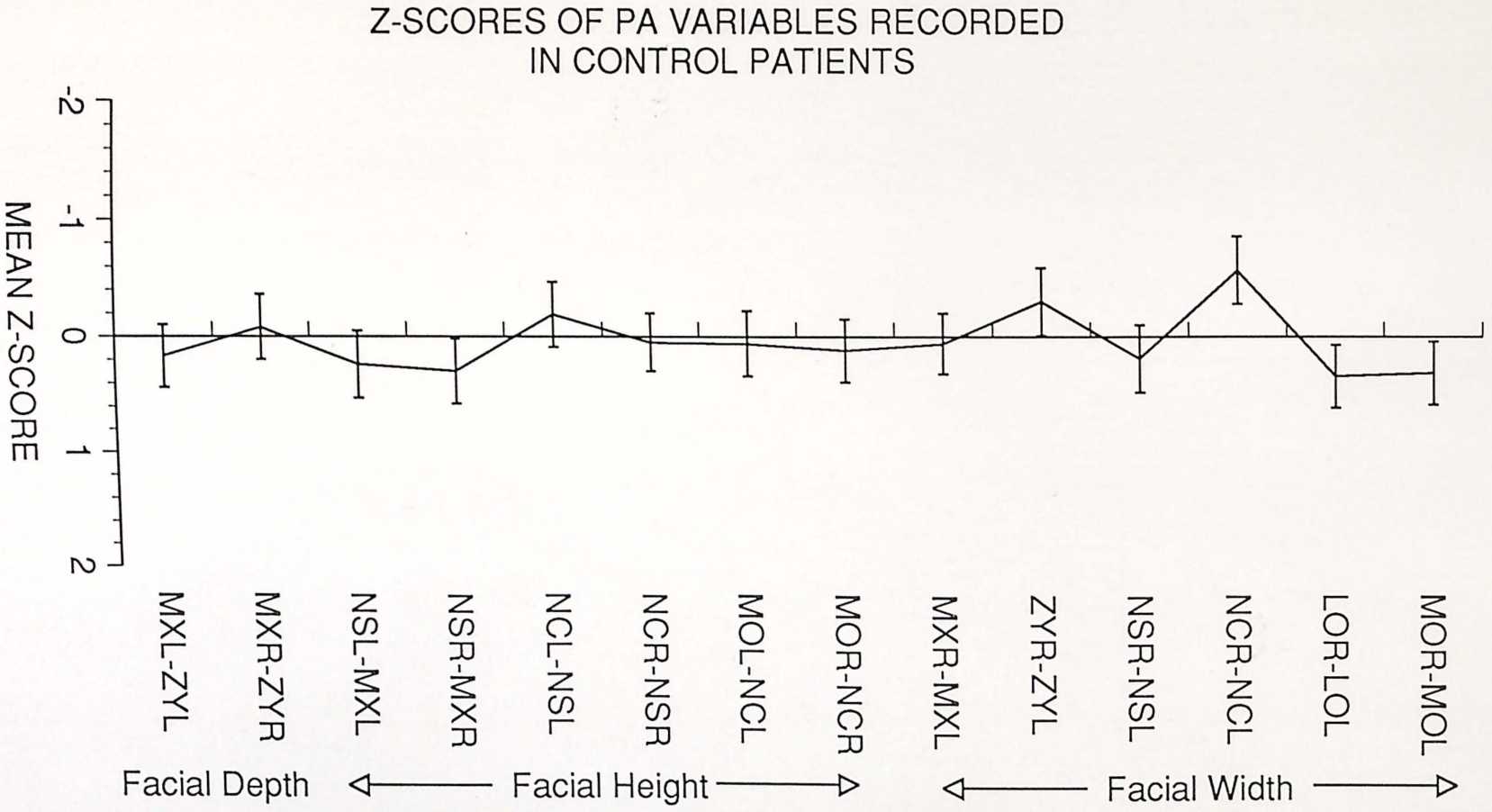

FIGURE 24. Mean Z-score pattern profile (with standard errors) of variables from PA radiographs for 10 randomly selected "normal" patients taken from an orthodontic patient file. The zero baseline represents the unaffected population mean for the 14 variables as reported by Saksena (1990).

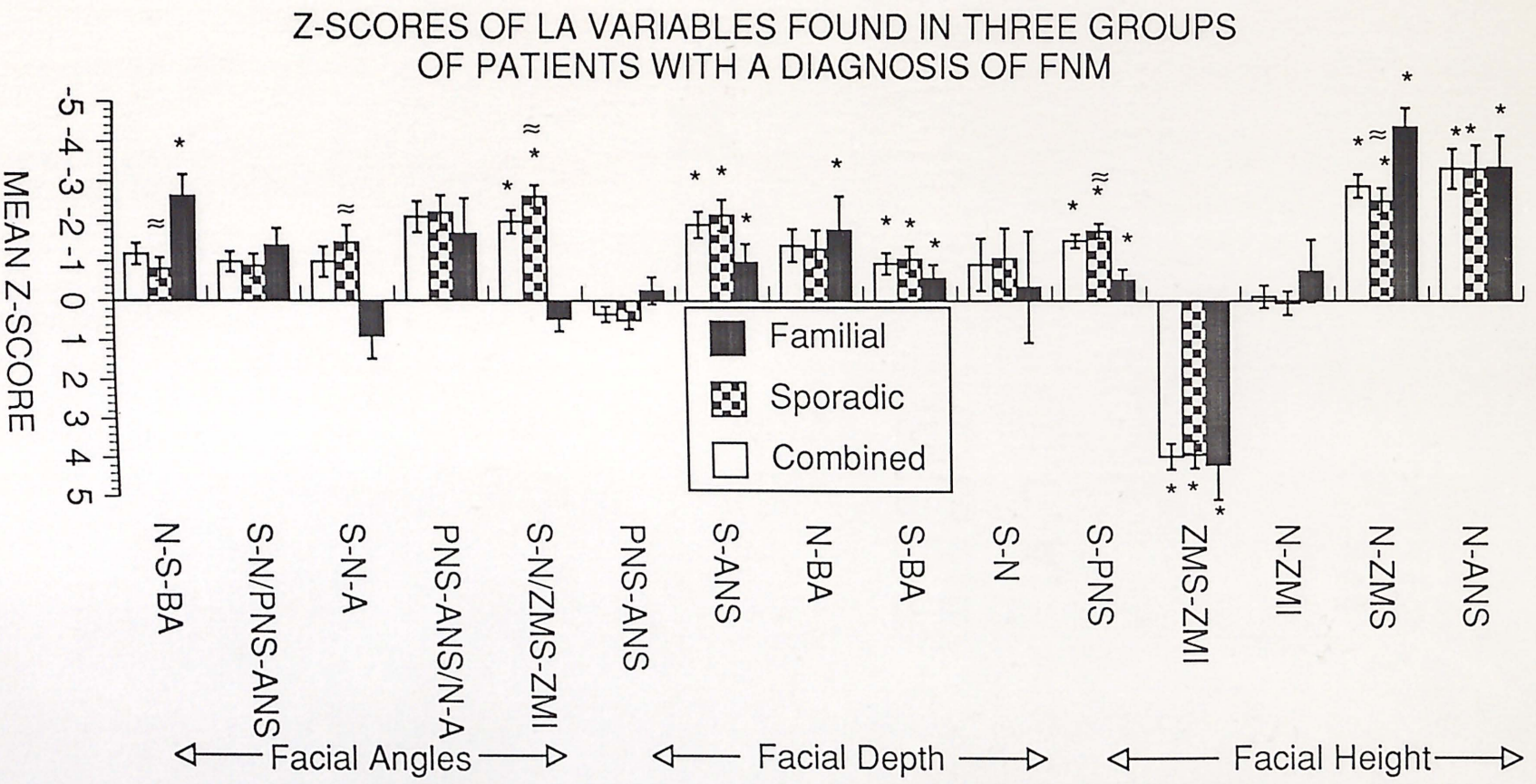

FIGURE 25. Mean Z-score pattern profiles of LA radiograph variables (with standard errors) for three subgroups of patients affected with FNM. The three subgroups are familial cases, sporadic cases, and all cases combined. The zero baseline represents the mean for the same 15 variables in an unaffected population as reported by Saksena et al. (1987). [* = significant difference from control and ≈ = significant difference from familial, $p<0.05$]

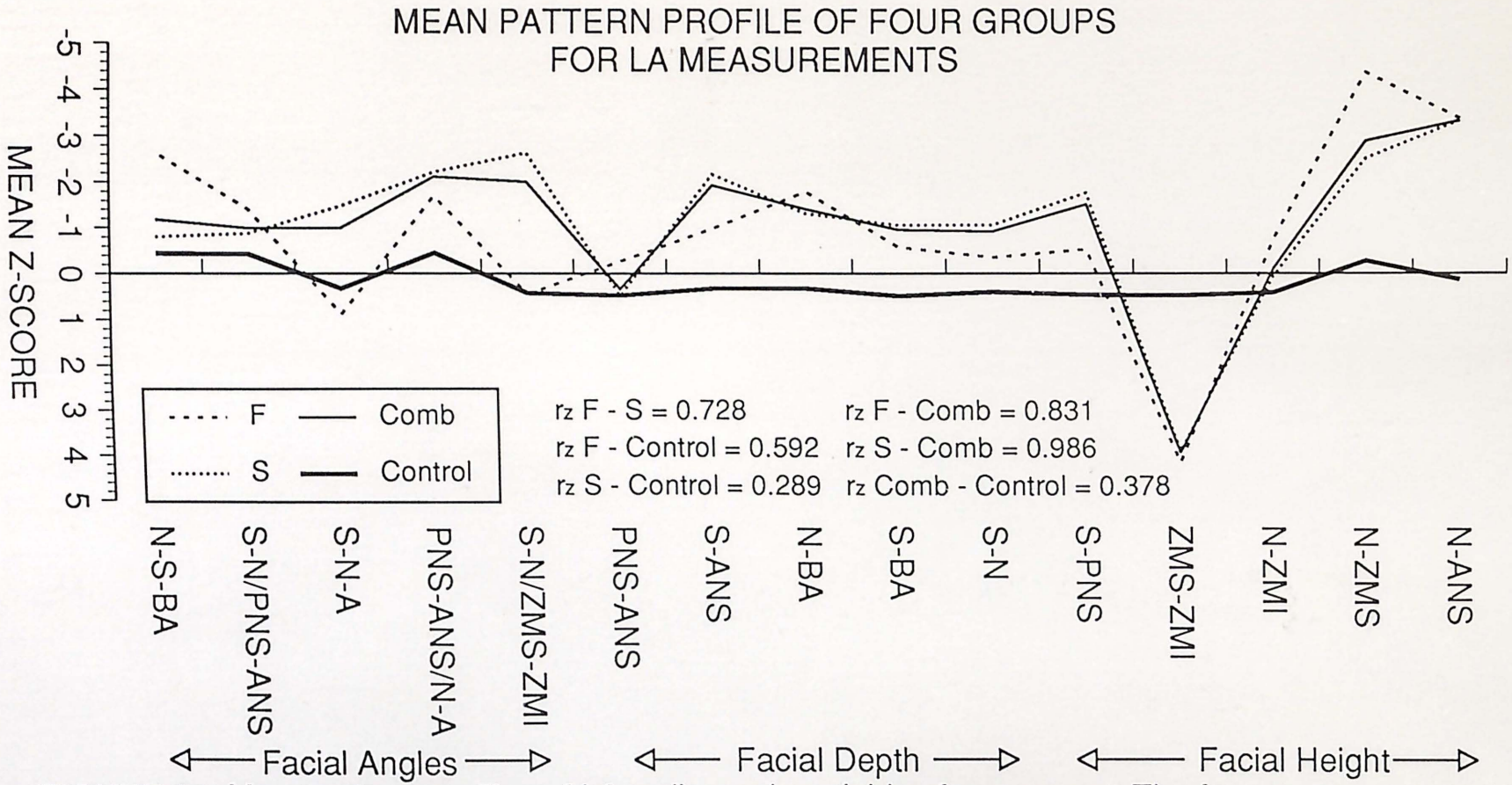

FIGURE 26. Mean pattern profiles of LA radiograph variables four groups. The four groups are familial cases of FNM (n = 11), sporadic cases of FNM (n = 43), all cases of FNM combined (n = 54), and a group of unaffected control patients from an orthodontic patient base (n = 10). The zero baseline represents the mean for the same variables in an unaffected population as reported by Saksena et al. (1987). The value r_z is a measure of pattern similarity; 1.0 represents a perfect correlation and 0 represents no correlation.

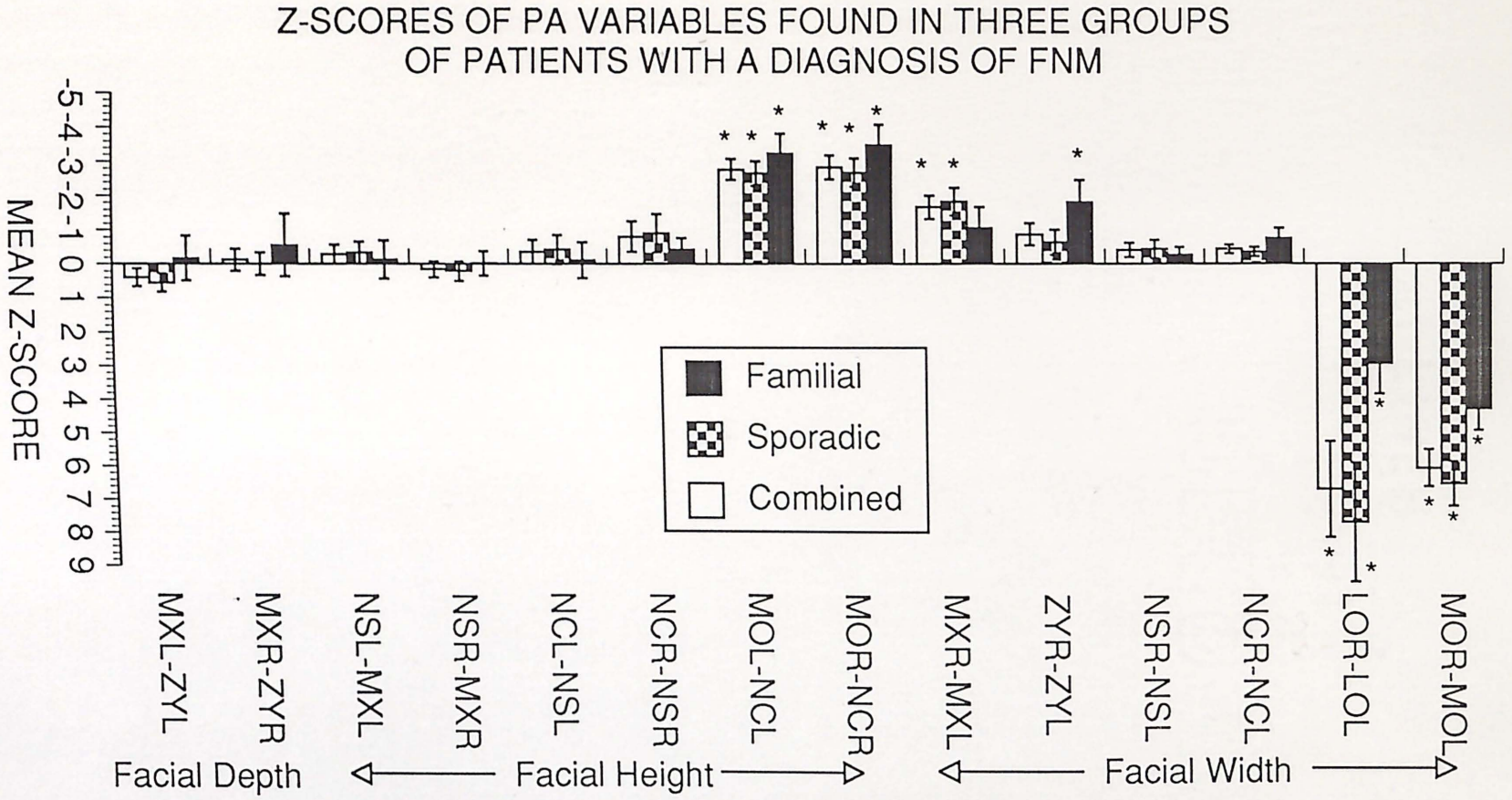

FIGURE 27. Mean Z-score pattern profiles of PA radiograph variables (with standard errors) for three subgroups of patients affected with FNM. The three subgroups are familial cases, sporadic cases, and all cases combined. The zero baseline represents the mean for the same 14 variables in an unaffected population as reported by Saksena (1990). [* = significant difference from control, $p<0.05$; there were no significant differences between familial, sporadic, and combined]

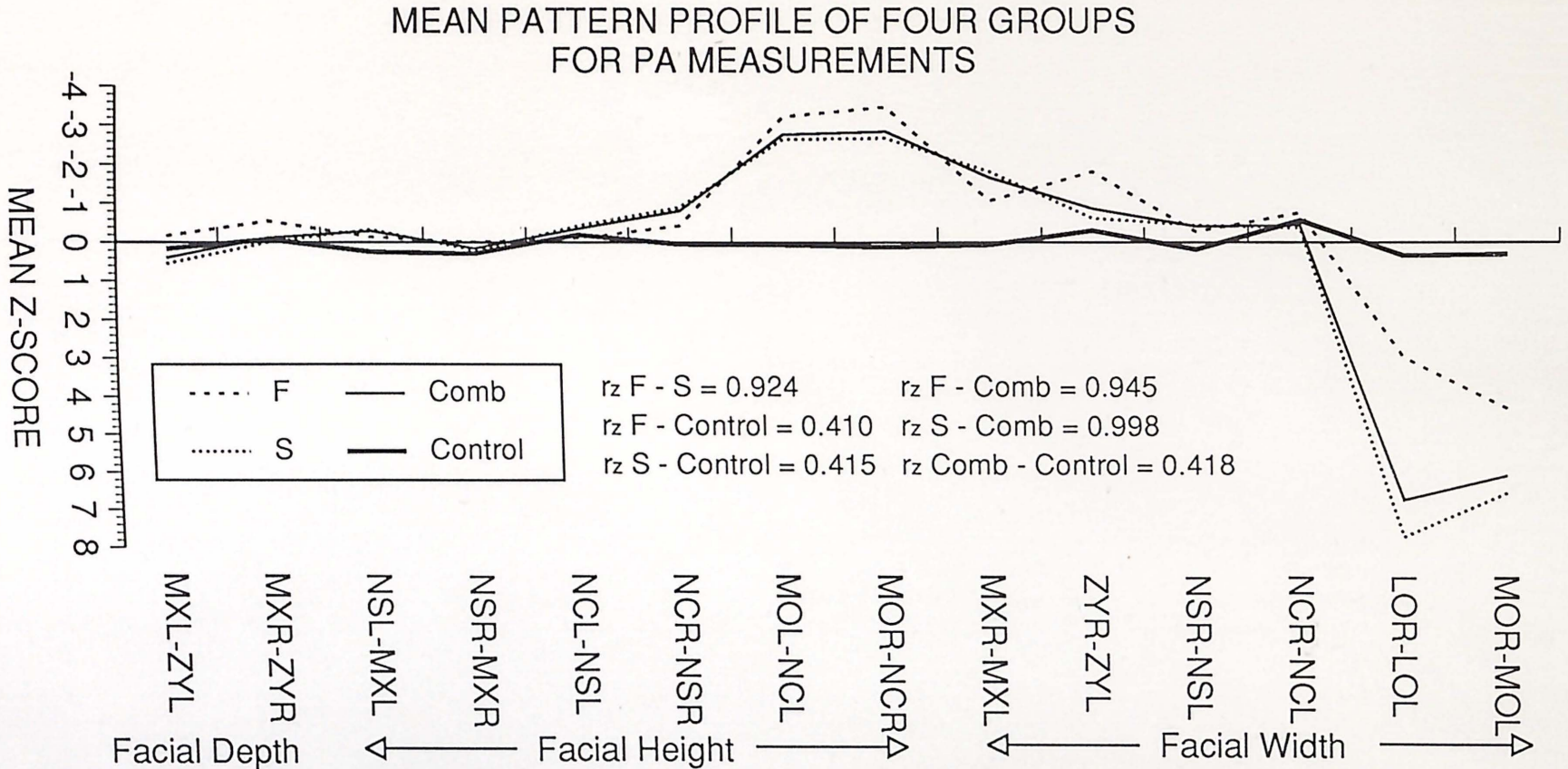

FIGURE 28. Mean pattern profiles of PA radiograph variables four groups. The four groups are familial cases of FNM (n = 10), sporadic cases of FNM (n = 38), all cases of FNM combined (n = 48), and a group of unaffected control patients from an orthodontic patient base (n = 10). The zero baseline represents the mean for the same variables in an unaffected population as reported by Saksena (1990). The value r_z is a measure of pattern similarity; 1.0 represents a perfect correlation and 0 represents no correlation.

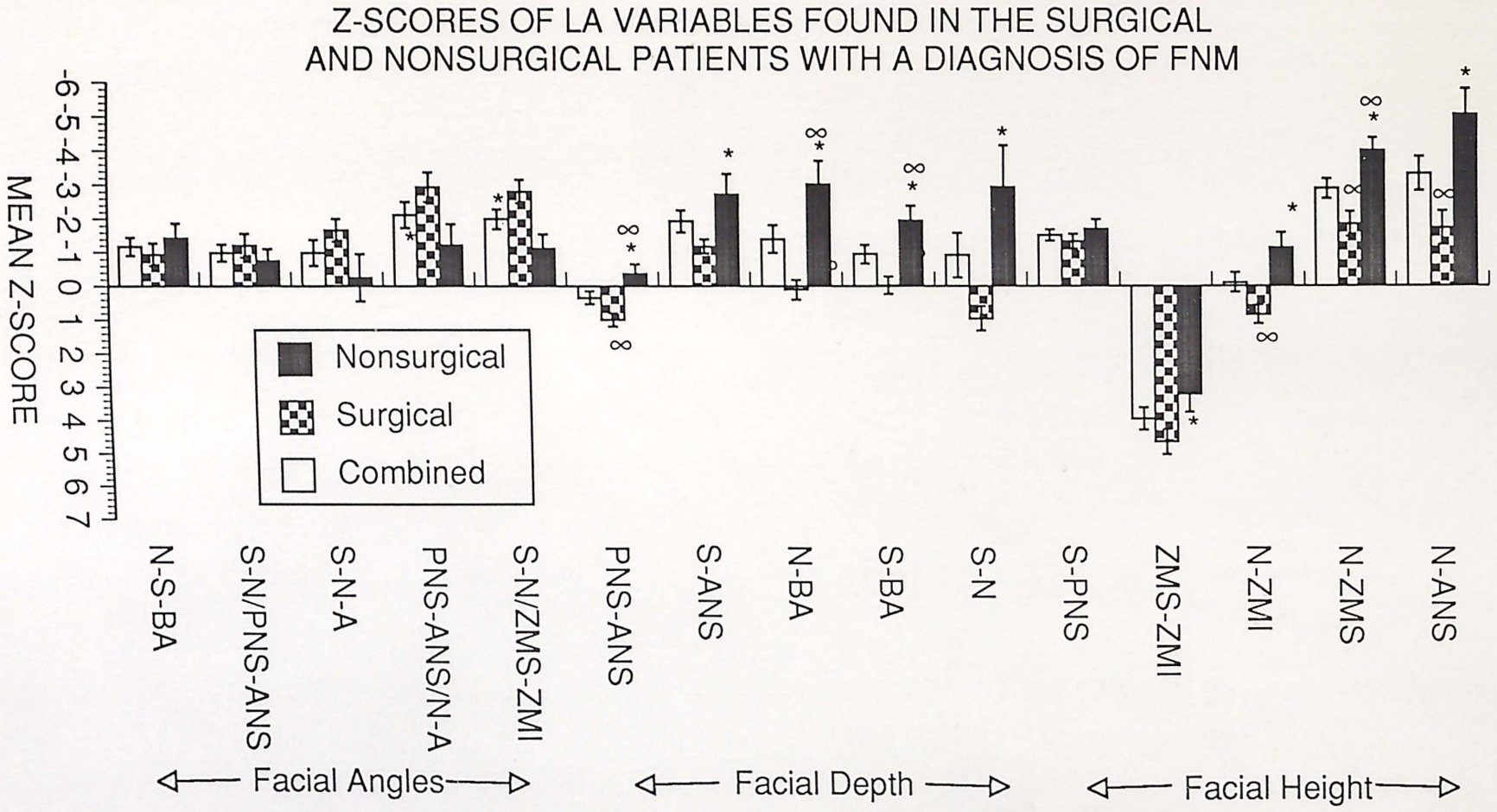

FIGURE 29. Mean Z-score pattern profile of LA radiographic variables with standard errors for three subgroups of patients affected with FNM. The three subgroups are surgical, nonsurgical, and all cases combined. The zero baseline represents the mean for the same 15 variables in an unaffected population as reported by Saksena et al. (1987). [* = significant difference from surgical, $p<0.05$; ∞ = significant difference from combined, $p<0.05$]

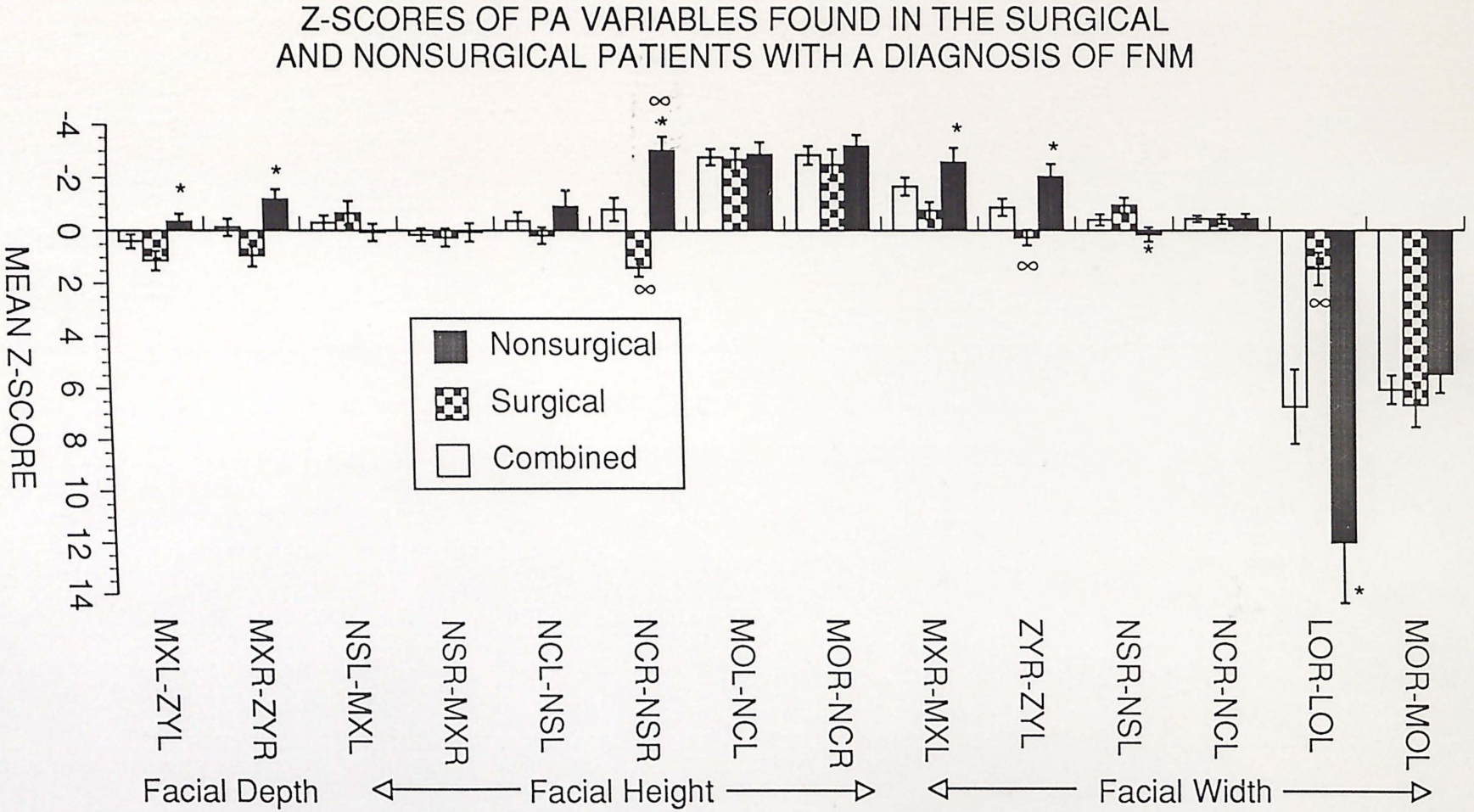

FIGURE 30. Mean Z-score pattern profile of PA radiographic variables with standard errors for three subgroups of patients with FNM. The three subgroups are surgical, nonsurgical, and all cases combined. The zero baseline represents the mean for the same 14 variables in an unaffected population as reported by Saksena (1990). [* = significant difference from surgical, $p<0.05$; ∞ = significant difference from combined, $p<0.05$]

TABLE I

LA facial landmarks and abbreviations

Abbreviation	Anatomic Name
S	Sella
NA	Nasion
BA	Basion
AR	Articulare
ZMS	Zygomaxillary Superior
ZMI	Zygomaxillary Inferior
PTM	Pterygomaxillary Fissure Inferior
PNS	Posterior Nasal Spine
ANS	Anterior Nasal Spine
A pt	Subspinale

TABLE II

PA facial landmarks and abbreviations

Abbreviation	Anatomic Name
MOR	Medial orbital wall (right)
SOR	Superior orbital wall (right)
LOR	Lateral orbital wall (right)
ZYR	Zygoma (right)
MXR	Maxilla (right)
NCR	Nasal cavity (right)
NSR	Nasal shelf (right)
MOL	Medial orbital wall (left)
SOL	Superior orbital wall (left)
LOL	Lateral orbital wall (left)
ZYL	Zygoma (left)
MXL	Maxilla (left)
NCL	Nasal cavity (left)
NSL	Nasal shelf (left)
SD	Supradentale
ID	Infradentale

TABLE III

LA facial measurements and abbreviations

Facial Height	
N-ANS	Middle anterior facial height
N-ZMS	Middle anterior facial height
N-ZMI	Middle anterior facial height
ZMS-ZMI	Middle anterior facial height
S-PNS	Middle posterior facial height

Facial Depth	
S-N	Anterior cranial base
S-BA	Posterior cranial base
N-BA	Effective cranial base
S-ANS	Maxillary position
PNS-ANS	Maxillary length

Facial Angles	
S-N/ZMS-ZMI	Anterior cranial base to zygomaxillary process
PNS-ANS/N-A	Maxillary angle
S-N-A	Maxillary horizontal position
S-N/PNS-ANS	Maxillary angle
N-S-BA	Cranial flexure

TABLE IV

PA facial measurements and abbreviations

Facial Width	
MOR-MOL	Interorbital width (Medial Orbital)
LOR-LOL	Interorbital width (Lateral Orbital)
NCR-NCL	Nasal cavity width
NSR-NSL	Nasal shelf width
ZYR-ZYL	Bizygomatic width
MXR-MXL	Bimaxillary width

Facial Height	
MOR-NCR	Middle facial height (right)
MOL-NCL	Middle facial height (left)
NCR-NSR	Nasal cavity wall to nasal shelf (right)
NCL-NSL	Nasal cavity wall to nasal shelf (left)
NSR-MXR	Nasal shelf to maxillary notch (right)
NSL-MXL	Nasal shelf to maxillary notch (left)

Facial Depth	
MXR-ZYR	Middle facial depth (right)
MXL-ZYL	Middle facial depth (left)

DISCUSSION

INTRAEXAMINER RELIABILITY

For both the LA and PA radiographs, the intraexaminer reliability was high with no significant differences between trials of the same examiner, or intraexaminer variability. The level of measurement error was consistent with previous studies[150-154] in that there were no statistically significant differences ($p > 0.05$)[155] between first, second, and third measurements for any variable as noted in Figures 19 and 20, and Appendices A and B. Therefore, there is good examiner reproducibility and consistency and low variability.

INTEREXAMINER RELIABILITY

There were no statistical differences between the three examiners. The level of measurement error was consistent with previous studies[150-154] in that there were no statistically significant differences ($p > 0.05$)[155] between first, second, and third examiners for any variable as noted in Figures 21 and 22, and Appendices C and D. This suggests that there is high reliability in the identification of the landmarks and reproducability of measurements.

CONTROL POPULATION COMPARED TO PUBLISHED NORMALS

The control population randomly selected from the orthodontic patient base is representative of the "normal" population reported by Saksena et al.[144] and Saksena.[145] Normal bell curve distribution curve places 68 percent of all values within one standard deviation of the mean and 95 percent of all values lie within two standard deviations of the mean. Figures 23 and 24 show that the standard error bars for each measurement showed little variation for this particular control population outside of 0.5 standard deviation for both LA and PA measurements. Therefore, the population selected for a control sample provided a valid standard for comparative purposes.

FRONTONASAL MALFORMATION PATIENTS COMPARED TO CONTROL POPULATIONS, LA AND PA MEASUREMENTS

The published literature on FNM makes no distinction between familial and sporadic cases other than the reporting of a positive or noncontributory family history. Initially, it was assumed that all cases of FNM were of a single causation and therefore should be grouped as a single unit for comparison to the controls. This grouping allows for a complete craniofacial pattern profile to be determined for the malformation a single entity. The results show that the face of the FNM patient is unique and significantly different from the control population.

LA Measurements

Although there are almost no changes in the midfacial height as measured by N-ZMI, anterior midfacial height is increased significantly in the zygomaxillary region (ZMS-ZMI). This could be interpreted as an attempt to compensate for the midfacial height deficiency by excess growth in the adjacent areas. Midfacial facial height is decreased significantly from the normals as observed in other measurements. The anterior portion (N-ANS and N-ZMS) and the posterior portion (S-PNS) were both shortened to yield a total midface deficiency. Incidently, the PA data suggested a shortened middle facial height as well (MO-NC bilaterally). Midface deficiency was diminished in a horizontal direction as well (S-ANS) with a shortened maxillary position. This horizontal dimension is not due to a decrease in maxillary length; in fact, it appears that the patients have attempted to compensate for the shortened maxillary position by slightly increasing the length of the maxilla itself (PNS-ANS). Other maxillary measurements were diminished as well. The maxillary position to cranial base (PNS-ANS/N-A), the maxillary anterior-posterior position (S-N-A), and the maxillary angle (S-N/PNS-ANS) were all smaller, although not significantly different from the controls.

The cranial base of an FNM patient contributes a different face from the control populations. The posterior cranial base (S-BA) is significantly decreased in the total population of FNM patients. The anterior part of the cranial base (S-N) and the effective length of the cranial base (N-BA) slightly compensated for the shorter posterior

cranial base length. These two measurements also were smaller than the controls, however, neither was significantly different from its corresponding control population. The cranial flexure angle (N-S-BA) was decreased but was not significantly different from the control population. Also, the angle between anterior cranial base and the zygomaxillary process (S-N/ZMS-ZMI) was significantly smaller than the control population.

PA Measurements

As expected, interorbital width (MOR-MOL and LOR-LOL) was significantly increased compared to the control population, although there was great variability seen. This hypertelorism was possibly compensated by the significantly diminished maxillary width. Similar to the facial height findings in the LA measurements, the middle facial height (MOR-NCR and MOL-NCL) in the PA also was significantly decreased. All other measurements, facial width, height, and depth, were not significantly different from the control population.

Correlations

As expected, the face of the FNM patient is quite different from that of the control population. The craniofacial pattern profile of the pooled population produces a correlation coefficient of 0.378 from the LA measurements and 0.418 from the PA measurements. These

values indicate that there is not a strong correlation between the two facial phenotypes.

FAMILIAL AND SPORADIC FRONTONASAL MALFORMATION SUBGROUPS COMPARED TO CONTROL POPULATIONS, LA AND PA MEASUREMENTS

Overall, the familial and the sporadic subgroups showed similar pattern profiles as compared with the total FNM sample. This may be anticipated and would be logical because the combined group is essentially the weighted average of the familial and the sporadic groups. Whether the familial or sporadic subgroups demonstrated significant differences in the face from the combined group is discussed below.

LA Measurements

Considering the LA measurements, the familial and sporadic groups resembled the combined cases. Again, for both familial and sporadic cases, middle facial height was decreased significantly in the anterior and the posterior dimension, while the middle anterior facial height in the zygomatic region compensated with significantly increased length. Also, the posterior cranial base length was shortened; furthermore, the maxillary position was retropositioned. This is similar to the observations of the combined group. Interestingly, that is the end of the similarities in the LA measurements. Only the familial cases exhibited a significantly

smaller mean cranial base length and cranial flexure angle. These particular findings have remarkable similarity to those of other syndromes. Grayson et al.[156] studied the cranial flexure angle by looking at the relationship of nasion, sella, and basion. They saw that in Apert's syndrome, the cranial flexure angle was compressed 12 percent, and the same angle was compressed 15 percent in Crouzon syndrome; there was no difference in Pfeiffer syndrome, craniofacial microsomia, and Treacher Collins syndrome. They also looked at FND and noticed that these patients also had a decreased cranial flexure angle and cranial base length.

The familial cases revealed a slight increase in the anterior cranial base to zygomaxillary process, although the combined and the sporadic cases demonstrated a significant decrease in the angular measurement. Only the familial cases had an increase in the maxillary angle, whereas the sporadic and the combined patients had a decrease in this angle. However, none of the subgroups was significantly different from each other.

PA Measurements

In the PA measurements, mean values of both familial and sporadic cases were not significantly different from the combined group for all measurements except for the zygomatic width. In this area of the face, only familial cases was significantly decreased when compared to both the control groups. The familial and sporadic cases mirrored the combined groups with an increase in interorbital width

and a decrease in the maxillary width and middle facial height. These findings may suggest that with time the familial cases have a pattern of growth and development that attempts to compensate more than the sporadic cases for the hypertelorism, however, the diminished modifcations in the zygomatic and maxillary width is not fully understood. It would be expected that regions near the areas of hypertelorism would be increased as well. The presence of craniosynostosis in this population may affect the circum-maxillary suture system. Spyropoulos and Burdi[157] commented that since there is premature fusion of one or more sutures, the growth and development of the face may result in a "wedging effect" so that there is the decrease in maxillary and zygomatic width. The growth in the cranium is restricted by the synostosis, but the lateral forces on the immovable basicranium drives the inferiorly positioned facial bones medially. This is supported by the observations of Newman and Burdi[158] who noticed that synostosis of the circum-maxillary suture system affects the morphogenic fields, the deeper capsular field and the more external morphogenic alar field, in those patients with severe facial clefting.

Correlations

Calculation of the correlation coefficients for LA measurements depicted an overall picture that the sporadic group had the least correlation with the control group ($r_z = 0.289$), while the LA familial showed somewhat higher correlation ($r_z = 0.592$). This trend is

reversed with the PA, although the difference is certainly not quite as great. The familial and sporadic cases showed correlation values of r_z = 0.410 and r_z = 0.415, respectively. This suggests that the sporadic cases are less correlated than the familal cases in their appearance with the control population; the familial cases may not be as severely affected as those that occur sporadically. This tends to support the general idea that when there is an anomaly that has a genetic predisposition present, it is less severe in the deformity than what occurs randomly. This takes into account the idea that the individuals with an anomaly are not as likely to reproduce and pass it to their offspring.

COMPARISONS AMONG FAMILIAL, SPORADIC, AND COMBINED SUBGROUPS

Another point of discussion centered around the determination whether the familial cases were different than the sporadic and the combined groups, and whether the sporadic cases were different than the familial and the combined groups. The correlation coefficients for the various PA groups, comparing familial versus sporadic, familial versus combined, and sporadic versus combined, all showed high degrees of correlation, i.e., r_z = 0.924, 0.945, and 0.998, respectively. The PA data show that there is no difference among any two of these three groups. The LA data suggested that some facial elements may be different in the familial group. The familial cases are significantly different from the combined group in four measurements: (1) the familial group is significantly shorter than

the combined group in middle anterior facial height (N-ZMS) and cranial flexure angle; (2) the familial cases are significantly larger than the combined group in the middle posterior facial height and the anterior cranial base to zygomaxillary process; (3) the sporadic cases and combined cases were completely alike in all of the LA measurements, however, they are significantly larger than the familial in the middle anterior facial height (N-ZMS) and cranial base flexure angle; and (4) sporadic cases are significantly smaller than the familial cases in the middle posterior facial height and the anterior cranial base to zygomaxillary process.

These results tend to suggest that there may be a real difference between the familial cases and the sporadic and/or combined groups. The correlation coefficient of the familial cases with the sporadic cases in the LA measurements is moderately high at $r_z = 0.728$ and even higher with the combined group at $r_z = 0.831$. Also, the sporadic and combined groups show a very high correlation, almost identity, of $r_z = 0.986$ between the two groups.

COMPARISONS BETWEEN NONSURGICAL AND SURGICAL SUBGROUPS

The severity of FNM from one patient to the next is quite variable as seen in Figures 1 through 11. Some of the patients in this affected population required extensive surgical procedures to correct severe anomalies, whereas others only needed limited surgical procedures for their condition. The surgical procedures ranged from the relatively simple procedure of opening a coronal suture for cranial

synostosis to the much more complex midfacial repositioning of the orbits. Considering the fact that there is extensive variability in the severity of the anomaly and the surgical procedures needed, the affected patient population is skewed somewhat.

Regardless, if the combined population is divided into the patients with and without surgical procedures as evidenced by wire, plates, or screws, eighteen measurements showed significant differences. Considering the LA and PA radiographs, twelve measurements demonstrated surgical improvement. It should be noted, however, that two of the PA measurements showed the surgical improvement unilaterally. The remaining six measurements for LA and PA radiographs demonstrated surgical impairment with only one PA measurement showing this unilateral effect.

EXPLANATION OF FINDINGS

The results of this study can be integrated into a series of statements that are deduced from the findings. Patients with FNM appear to have a midfacial deficiency in height and depth. This is supported by the findings that the anterior and posterior facial height in the LA and PA cephalograms are decreased. Decreased posterior facial depth at the cranial base and maxillary retroposition may sustains the overall illusion of midface deficiency.

The facial height in the zygomatic region is increased. This may be a compensation for the midface deficiency. The zygomatic buttress in the FNM patient seems longer. The ZMI appears to be

positioned posteriorly, and together with the lengthening, these combine to create an aberrant angle with the anterior cranial base.

The third key finding is that the interorbital width is increased in the patients with FNM. This supports previous case reports of patients with hypertelorism. The size of the orbital socket itself appears to be increased as well. It would be expected that the maxillary region would be increased somewhat due to its close proximity to the increased orbital region. The associated morphometric findings in the FNM patient that shows there is a decrease in the maxillary width actually compounds the deficiency. These findings cannot be explained.

When the FNM patients are divided into familial and sporadic subgroups, the familial patients with FNM have a shorter anterior facial height and a smaller cranial flexure angle. However, the same familial cases demonstrate larger dimensions than sporadic cases in regard to maxillary position and in the anterior cranial base/zygomatic angle. This suggests that the familial cases have a flatter cranial base than the sporadic patients. As the cranial base flattens, the cranial flexure angle would decrease and the maxilla would seem to be positioned further anteriorly. Also, facial height decreases, and the cranial base/zygomatic buttress angle would increase. The PA measurements further suggest that the familial cases have a narrower zygomatic region to compensate for the increased interorbital width than do the sporadic cases.

Finally, when the affected population of FNM is divided into nonsurgical and surgical patients, the advantageous effects of surgery are seen more than the deleterious effects. The spectrum of

surgical procedures utilized for patients with FNM enable the surgeon to improve the craniofacial structures of these patients to achieve a more "normal" appearing face. The typical growth of the FNM patients often requires surgical help to achieve the desired facial characteristics.

SUMMARY AND CONCLUSIONS

This study investigated the craniofacial morphology in familial and sporadic cases of the rare frontonasal malformation (FNM). The ultimate purpose was describe the facial characteristics of the FNM patient and differentiate it from the so-called "normal" population using well established cephalometric methodology. This information could be beneficial in carrying out the differential diagnostic workup for people with FNM or similar syndromes, as well as very helpful in predicting and counseling affected people about their genetic liability for offspring with FNM.

Fourteen patients affected with FNM in 10 families participated. LA and PA cephalographs were taken on each individual. The radiographs were digitized, then multiple linear and angular measurements of craniofacial structures were made. By converting raw data to Z-scores, non-linear effects of growth manifested by age and sex differences were essentially eliminated. All affected patients were combined to determine if there were differences between the "normal" control population and the entire group with FNM. The patients were then divided into either familial or sporadic subgroups based upon their family history, and into either surgical or nonsurgical subgroups based upon their surgical history.

Univariate analysis of variance and Student-Newman-Keuls tests compared the mean Z-scores for 29 variables. In the pooled FNM radiographs, eight measurements were significantly different from the control population. Specifically, the following measurements

were found to be significantly decreased in all patients of FNM: anterior facial height (N-ANS and N-ZMS), posterior facial height (S-PNS), facial depth in the posterior cranial base (S-BA), middle facial depth (S-ANS), the facial angle of S-N/ZMS-ZMI, and facial height (MOR-NCR and MOL-NCL). Facial height in the zygomatic region (ZMS-ZMI) and interorbital width (MOR-MOL and LOR-LOL) were increased in the FNM pool.

Concerning the differences between the familial and sporadic subgroups, the familial patients were found to be significantly shorter than the sporadic patients in anterior facial height (N-ZMS) and the cranial flexure angle (N-S-BA); in contrast, the sporadic patients were significantly shorter than the familial patients in the maxillary position (S-N-A) and the facial angle of S-N/ZMS-ZMI. The patients with surgical procedures demonstrated twelve measurements with significant differences towards surgical improvement from the typical growth of those patients who did not have surgery.

The mean pattern profiles illustrate the basic differences in the facial morphology between the control population, the combined group of FNM patients, and between the familial and sporadic subgroups. The data from this research suggests that patients with FNM, regardless of any genetic or sporadic predisposition, have a midface deficiency in height and depth, an increased interorbital width with possible increased orbital socket width, and a longer zygomatic buttress. Futher, the familial cases tend to have a flatter cranial base than the sporadic cases. Finally, the familial patients show narrower zygomatic widths than sporadic cases with FNM.

In conclusion, the hypothesis that the face of a patient with frontonasal malformation is different from the "normal" control population is supported by this research. Distinctive differences occur in eleven variables. Comparing the pattern profiles and correlation coefficients of the FNM patients with the other clinical entities listed in this study, it appears that FMN is a distinct clinical syndrome that has a specific radiographic appearance that is unique to this patient population. The difference between the familial and sporadic groups of patients can be characterized by only four variables. In turn, this tends to support the general idea that when there is an anomaly, or specifically FNM, that has a genetic predisposition present, it is less severe in the deformity than what occurs in FNM as sporadic event. By employing a cephalometric analysis, individuals could be correctly diagnosed with FNM versus other, yet similar, syndromes. In the future, other syndromes need to cephalometrically defined, and the differences between these syndromes could be evaluated by the comparison of the correlation coefficients. These findings should prove helpful in isolating those patients with frontonasal malformation from the differential diagnosis and in their genetic counseling.

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APPENDIX

APPENDIX A

INTRAEXAMINER RELIABILITY TEST MEAN Z-SCORES, STANDARD DEVIATIONS (σ_z), STANDARD ERRORS, AND ANOVA F AND P VALUES FOR LA MEASUREMENTS

LA	Trial 1 (n = 10)			Trial 2 (n = 10)			Trial 3 (n = 10)			ANOVA	
Measurement	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	F value	P Value
Facial Height											
N-ANS	-1.65	2.48	0.78	-1.67	2.46	0.78	-1.65	2.44	0.77	0.000	1.000
N-ZMS	-2.04	1.90	0.60	-2.12	1.83	0.58	-2.02	1.97	0.62	0.008	0.992
N-ZMI	0.99	1.26	0.40	0.87	1.26	0.40	1.00	1.29	0.41	0.033	0.968
ZMS-ZMI	3.87	1.78	0.56	3.77	1.66	0.53	3.81	1.86	0.59	0.007	0.993
S-PNS	-1.23	1.19	0.38	-1.24	1.21	0.38	-1.20	1.17	0.37	0.003	0.997
Facial Depth											
S-N	1.01	2.57	0.81	0.94	2.67	0.85	0.88	2.73	0.86	0.007	0.993
S-BA	0.23	0.88	0.28	0.21	0.91	0.29	0.27	0.93	0.29	0.014	0.986
N-BA	-0.13	1.25	0.39	-0.08	1.33	0.42	-0.04	1.24	0.39	0.015	0.986
S-ANS	-0.68	1.21	0.38	-0.65	1.15	0.36	-0.72	1.12	0.35	0.010	0.990
PNS-ANS	0.96	1.09	0.34	0.94	1.06	0.33	0.97	1.06	0.34	0.002	0.998
Facial Angles											
S-N/ZMS-ZMI	-1.94	2.15	0.68	-1.94	2.22	0.70	-1.96	2.25	0.71	0.000	1.000
PNS-ANS/N-A	-2.34	1.68	0.53	-2.34	1.69	0.53	-2.34	1.81	0.57	0.000	1.000
S-N-A	-1.11	1.95	0.62	-1.08	1.99	0.63	-1.12	2.02	0.64	0.002	0.999
S-N/PNS-ANS	-1.66	1.69	0.53	-1.83	1.76	0.56	-1.71	1.81	0.57	0.023	0.977
N-S-BA	-1.32	1.06	0.33	-1.37	1.10	0.35	-1.33	1.06	0.34	0.007	0.994

There are no significantly different mean Z-scores within the examiner.

APPENDIX B

INTRAEXAMINER RELIABILITY TEST MEAN Z-SCORES, STANDARD DEVIATIONS (σ_z), STANDARD ERRORS, AND ANOVA F AND P VALUES FOR PA MEASUREMENTS

PA	Trial 1 (n = 10)			Trial 2 (n = 10)			Trial 3 (n = 10)			ANOVA	
Measurement	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	F value	P Value
Facial Width											
MOR-MOL	5.77	2.64	0.83	5.74	2.57	0.81	5.68	2.59	0.82	0.004	0.996
LOR-LOL	1.95	3.34	1.05	1.91	3.38	1.07	1.87	3.41	1.08	0.001	0.999
NCR-NCL	-0.84	0.76	0.24	-0.82	0.76	0.24	-0.90	0.78	0.25	0.029	0.972
NSR-NSL	-0.85	1.44	0.46	-0.83	1.50	0.47	-0.82	1.41	0.45	0.001	0.999
ZYR-ZYL	0.01	1.38	0.44	0.00	1.38	0.44	-0.03	1.42	0.45	0.002	0.998
MXR-MXL	-0.35	1.51	0.48	-0.32	1.41	0.45	-0.31	1.43	0.45	0.003	0.998
Facial Height											
MOR-NCR	-3.16	1.62	0.51	-3.21	1.68	0.53	-3.21	1.69	0.53	0.004	0.996
MOL-NCL	-2.66	1.68	0.53	-2.65	1.67	0.53	-2.63	1.63	0.52	0.001	0.999
NCR-NSR	0.36	1.45	0.46	0.33	1.45	0.46	0.36	1.49	0.47	0.002	0.998
NCL-NSL	-0.28	1.18	0.37	-0.33	1.22	0.39	-0.31	1.16	0.37	0.005	0.995
NSR-MXR	0.64	1.74	0.55	0.58	1.76	0.56	0.71	1.79	0.57	0.013	0.987
NSL-MXL	-0.86	2.55	0.80	-0.79	2.58	0.81	-0.82	2.54	0.80	0.002	0.998
Facial Depth											
MXR-ZYR	0.95	2.00	0.63	0.99	2.05	0.65	1.07	2.13	0.67	0.008	0.992
MXL-ZYL	1.70	2.11	0.67	1.67	2.08	0.66	1.65	2.09	0.66	0.002	0.998

There are no significantly different mean Z-scores within the examiner.

APPENDIX C

INTEREXAMINER RELIABILITY TEST MEAN Z-SCORES, STANDARD DEVIATIONS (σ_z), STANDARD ERRORS, AND ANOVA F AND P VALUES FOR LA MEASUREMENTS

LA	Examiner 1 (n = 10)			Examiner 2 (n = 10)			Examiner 3 (n = 10)			ANOVA	
Measurement	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	F value	P Value
Facial Height											
N-ANS	-1.65	2.48	0.78	-1.60	2.51	0.79	-1.59	2.51	0.79	0.002	0.998
N-ZMS	-2.04	1.90	0.60	-1.91	1.69	0.53	-2.21	1.59	0.50	0.100	0.925
N-ZMI	0.99	1.26	0.40	0.85	1.44	0.45	0.78	1.53	0.48	0.100	0.945
ZMS-ZMI	3.87	1.78	0.56	3.91	1.74	0.55	3.89	1.67	0.53	0.002	0.998
S-PNS	-1.23	1.19	0.38	-1.29	1.34	0.42	-1.22	1.21	0.38	0.010	0.990
Facial Depth											
S-N	1.01	2.57	0.81	1.05	2.79	0.88	1.06	2.79	0.88	0.001	0.999
S-BA	0.23	0.88	0.28	0.28	0.90	0.29	0.30	0.99	0.31	0.100	0.940
N-BA	-0.13	1.25	0.39	-0.10	1.29	0.41	-0.05	1.33	0.42	0.010	0.991
S-ANS	-0.68	1.21	0.38	-0.73	1.19	0.38	-0.76	1.10	0.35	0.012	0.988
PNS-ANS	0.96	1.09	0.34	0.89	0.98	0.31	0.92	1.10	0.35	0.010	0.990
Facial Angles											
S-N/ZMS-ZMI	-1.94	2.15	0.68	-1.99	2.32	0.73	-1.81	2.18	0.69	0.017	0.983
PNS-ANS/N-A	-2.34	1.68	0.53	-2.28	1.78	0.56	-2.34	1.90	0.60	0.003	0.997
S-N-A	-1.11	1.95	0.62	-1.04	2.01	0.64	-1.05	2.01	0.64	0.004	0.996
S-N/PNS-ANS	-1.66	1.69	0.53	-1.74	1.75	0.55	-1.69	1.86	0.59	0.006	0.994
N-S-BA	-1.32	1.06	0.33	-1.40	1.12	0.35	-1.40	1.00	0.32	0.019	0.981

There are no significantly different mean Z-scores between each examiner.

APPENDIX D

INTEREXAMINER RELIABILITY TEST MEAN Z-SCORES, STANDARD DEVIATIONS (σ_z), STANDARD ERRORS, AND ANOVA F AND P VALUES FOR PA MEASUREMENTS

PA Measurement	Examiner 1 (n = 10)			Examiner 2 (n = 10)			Examiner 3 (n = 10)			ANOVA	
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	F value	P Value
Facial Width											
MOR-MOL	5.77	2.64	0.83	5.78	2.57	0.81	5.78	2.57	0.81	0.002	0.998
LOR-LOL	1.95	3.34	1.05	1.83	3.35	1.06	1.83	3.35	1.06	0.004	0.996
NCR-NCL	-0.84	0.76	0.24	-0.88	0.82	0.26	-0.88	0.82	0.26	0.012	0.989
NSR-NSL	-0.85	1.44	0.46	-0.84	1.52	0.48	-0.84	1.52	0.48	0.003	0.997
ZYR-ZYL	0.01	1.38	0.44	0.03	1.44	0.46	0.03	1.44	0.46	0.002	0.998
MXR-MXL	-0.35	1.51	0.48	-0.31	1.40	0.44	-0.31	1.40	0.44	0.003	0.998
Facial Height											
MOR-NCR	-3.16	1.62	0.51	-3.23	1.68	0.53	-3.23	1.68	0.53	0.006	0.994
MOL-NCL	-2.66	1.68	0.53	-2.62	1.61	0.51	-2.62	1.61	0.51	0.002	0.998
NCR-NSR	0.36	1.45	0.46	0.37	1.48	0.47	0.37	1.48	0.47	0.003	0.998
NCL-NSL	-0.28	1.18	0.37	-0.31	1.27	0.40	-0.31	1.27	0.40	0.005	0.995
NSR-MXR	0.64	1.74	0.55	0.66	1.73	0.55	0.66	1.73	0.55	0.000	1.000
NSL-MXL	-0.86	2.55	0.80	-0.78	2.54	0.80	-0.78	2.54	0.80	0.004	0.996
Facial Depth											
MXR-ZYR	0.95	2.00	0.63	0.94	2.01	0.64	0.94	2.01	0.64	0.000	1.000
MXL-ZYL	1.70	2.11	0.67	1.70	2.13	0.67	1.70	2.13	0.67	0.002	0.998

There are no significantly different mean Z-scores between each examiner.

APPENDIX E

MEANS Z-SCORES, STANDARD DEVIATIONS (σ_z), AND STANDARD ERRORS FOR LA MEASUREMENTS

LA Measurement	Familial (n = 11)			Sporadic (n = 43)			Combined (n = 54)			Control (n = 10)		
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE
Facial Height												
N-ANS	-3.37	2.63	0.79	-3.32	3.91	0.60	-3.33	3.67	0.50	0.14	0.85	0.27
N-ZMS	-4.36	1.64	0.49	-2.51	2.14	0.33	-2.89	2.16	0.29	-0.28	0.85	0.27
N-ZMI	-0.75	2.64	0.79	0.05	1.99	0.30	-0.11	2.13	0.29	0.41	0.92	0.29
ZMS-ZMI	4.15	2.94	0.89	3.89	2.33	0.35	3.94	2.44	0.33	0.48	0.83	0.26
S-PNS	-0.53	0.85	0.26	-1.76	1.23	0.19	-1.51	1.26	0.17	0.46	0.63	0.20
Facial Depth												
S-N	-0.35	4.68	1.41	-1.06	4.98	0.76	-0.92	4.88	0.66	0.40	0.74	0.23
S-BA	-0.58	1.14	0.34	-1.05	2.18	0.33	-0.95	2.01	0.27	0.49	0.93	0.29
N-BA	-1.78	2.80	0.85	-1.31	3.11	0.47	-1.40	3.03	0.41	0.33	0.79	0.25
S-ANS	-0.98	1.53	0.46	-2.16	2.55	0.39	-1.92	2.41	0.33	0.32	0.71	0.22
PNS-ANS	-0.26	1.12	0.34	0.49	1.46	0.22	0.34	1.42	0.19	0.48	0.85	0.27
Facial Angles												
S-N/ZMS-ZMI	0.45	1.05	0.32	-2.62	1.82	0.28	-1.99	2.10	0.29	0.43	0.80	0.25
PNS-ANS/N-A	-1.70	2.92	0.88	-2.21	2.86	0.44	-2.11	2.85	0.39	-0.45	0.95	0.30
S-N-A	0.89	1.95	0.59	-1.47	2.83	0.43	-0.99	2.83	0.38	0.32	0.93	0.29
S-N/PNS-ANS	-1.40	1.41	0.43	-0.88	1.95	0.30	-0.99	1.85	0.25	-0.43	0.96	0.30
N-S-BA	-2.63	1.79	0.54	-0.81	1.88	0.29	-1.18	1.99	0.27	-0.44	0.76	0.24

APPENDIX F

MEANS Z-SCORES, STANDARD DEVIATIONS (σ_z), AND STANDARD ERRORS FOR PA MEASUREMENTS

PA Measurement	Familial (n = 10)			Sporadic (n = 38)			Combined (n = 48)			Control (n = 10)		
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE
Facial Width												
MOR-MOL	4.29	2.00	0.63	6.51	4.07	0.66	6.05	3.83	0.55	0.31	0.85	0.27
LOR-LOL	2.96	2.78	0.88	7.67	10.90	1.77	6.69	9.94	1.43	0.34	0.86	0.27
NCR-NCL	-0.76	0.92	0.29	-0.36	0.89	0.14	-0.44	0.90	0.13	-0.57	0.92	0.29
NSR-NSL	-0.27	0.68	0.22	-0.44	1.64	0.27	-0.41	1.49	0.21	0.19	0.92	0.29
ZYR-ZYL	-1.81	2.05	0.65	-0.63	2.30	0.37	-0.87	2.28	0.33	-0.30	0.92	0.29
MXR-MXL	-1.06	1.92	0.61	-1.82	2.47	0.40	-1.66	2.37	0.34	0.06	0.83	0.26
Facial Height												
MOR-NCR	-3.47	1.90	0.60	-2.67	2.52	0.41	-2.83	2.41	0.35	0.12	0.85	0.27
MOL-NCL	-3.22	1.84	0.58	-2.64	2.20	0.36	-2.76	2.12	0.31	0.06	0.87	0.28
NCR-NSR	-0.43	1.01	0.32	-0.90	3.44	0.56	-0.80	3.09	0.45	0.05	0.80	0.25
NCL-NSL	-0.11	1.65	0.52	-0.42	2.64	0.43	-0.35	2.45	0.35	-0.19	0.87	0.28
NSR-MXR	-0.02	1.13	0.36	0.21	1.79	0.29	0.16	1.66	0.24	0.30	0.90	0.28
NSL-MXL	-0.13	1.76	0.56	-0.33	1.99	0.32	-0.29	1.93	0.28	0.24	0.92	0.29
Facial Depth												
MXR-ZYR	-0.55	2.90	0.92	0.00	2.03	0.33	-0.12	2.22	0.32	-0.08	0.90	0.28
MXL-ZYL	-0.17	2.09	0.66	0.55	1.69	0.27	0.40	1.78	0.26	0.17	0.84	0.27

APPENDIX G

ANOVA P VALUES OF FOUR COMPARISONS BETWEEN TWO GROUPS OF LA MEASUREMENTS

LA Measurement	Combined Control	Familial Sporadic	Familial Control	Sporadic Control
Facial Height				
N-ANS	0.004*	0.966	0.001*	0.008*
N-ZMS	0.000*	0.010*	0.000*	0.002*
N-ZMI	0.455	0.268	0.203	0.587
ZMS-ZMI	0.000*	0.753	0.001	0.000*
S-PNS	0.000*	0.003*	0.008*	0.000*
Facial Depth				
S-N	0.400	0.671	0.621	0.362
S-BA	0.030*	0.496	0.030*	0.034*
N-BA	0.080	0.647	0.034*	0.108
S-ANS	0.005*	0.150	0.025*	0.004*
PNS-ANS	0.772	0.115	0.107	0.969
Facial Angles				
S-N/ZMS-ZMI	0.001*	0.000*	0.960	0.000*
PNS-ANS/N-A	0.075	0.598	0.211	0.061
S-N-A	0.155	0.012*	0.412	0.056
S-N/PNS-ANS	0.362	0.417	0.087	0.484
N-S-BA	0.256	0.005*	0.002*	0.554
Correlation Coefficient r_z	0.378	0.728	0.592	0.289

Note: * designates that there is a significant difference between the two groups at $p < 0.05$.

APPENDIX H

ANOVA P VALUES OF FOUR COMPARISONS BETWEEN TWO GROUPS OF PA MEASUREMENTS

PA Measurement	Combined Control	Familial Sporadic	Familial Control	Sporadic Control
Facial Width				
MOR-MOL	0.000*	0.103	0.000*	0.000*
LOR-LOL	0.050*	0.185	0.011*	0.040*
NCR-NCL	0.687	0.211	0.645	0.509
NSR-NSL	0.233	0.753	0.223	0.254
ZYR-ZYL	0.437	0.145	0.047*	0.660
MXR-MXL	0.028*	0.373	0.109	0.023*
Facial Height				
MOR-NCR	0.000*	0.354	0.000*	0.001*
MOL-NCL	0.000*	0.451	0.000*	0.000*
NCR-NSR	0.397	0.677	0.257	0.397
NCL-NSL	0.837	0.729	0.895	0.791
NSR-MXR	0.795	0.709	0.492	0.872
NSL-MXL	0.401	0.769	0.566	0.383
Facial Depth				
MXR-ZYR	0.959	0.494	0.630	0.909
MXL-ZYL	0.697	0.262	0.639	0.501
Correlation Coefficient r_z	0.418	0.924	0.410	0.415

Note: * designates that there is a significant difference between the two groups at $p < 0.05$.

APPENDIX I

ANOVA P VALUES OF THREE COMPARISONS BETWEEN TWO GROUPS OF LA MEASUREMENTS

LA Measurement	Nonsurgical Combined	Surgical Combined	Nonsurgical Surgical
Facial Height			
N-ANS	0.055	0.043*	0.001*
N-ZMS	0.024*	0.034*	0.000*
N-ZMI	0.053	0.037*	0.000*
ZMS-ZMI	0.223	0.198	0.030*
S-PNS	0.533	0.530	0.281
Facial Depth			
S-N	0.118	0.055	0.003*
S-BA	0.045*	0.033*	0.000*
N-BA	0.036*	0.017*	0.000*
S-ANS	0.216	0.132	0.019*
PNS-ANS	0.040*	0.035*	0.000*
Facial Angles			
S-N/ZMS-ZMI	0.088	0.089	0.003*
PNS-ANS/N-A	0.215	0.192	0.027*
S-N-A	0.326	0.253	0.068
S-N/PNS-ANS	0.590	0.608	0.365
N-S-BA	0.600	0.595	0.364

Note: * designates that there is a significant difference between the two groups at $p < 0.05$.

APPENDIX J

ANOVA P VALUES OF THREE COMPARISONS BETWEEN TWO GROUPS OF PA MEASUREMENTS

PA Measurement	Nonsurgical Combined	Surgical Combined	Nonsurgical Surgical
Facial Width			
MOR-MOL	0.532	0.556	0.297
LOR-LOL	0.050	0.014*	0.000*
NCR-NCL	0.997	0.997	0.995
NSR-NSL	0.131	0.141	0.009*
ZYR-ZYL	0.053	0.027*	0.000*
MXR-MXL	0.148	0.094	0.007*
Facial Height			
MOR-NCR	0.548	0.583	0.324
MOL-NCL	0.852	0.847	0.745
NCR-NSR	0.004*	0.002*	0.000*
NCL-NSL	0.415	0.324	0.125
NSR-MXR	0.821	0.823	0.699
NSL-MXL	0.424	0.471	0.191
Facial Depth			
MXR-ZYR	0.050	0.055	0.001*
MXL-ZYL	0.080	0.101	0.003*

Note: * designates that there is a significant difference between the two groups at $p < 0.05$.

ABSTRACT

CRANIOFACIAL PATTERN PROFILE ANALYSIS OF INDIVIDUALS WITH FRONTONASAL MALFORMATION

by

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Frontonasal malformation, FNM, was first described by Hoppe in 1859. FNM is an anomaly that is characterized by ocular hypertelorism, broad nasal root, lack of a nasal tip, V-shaped hair prolongation onto the forehead (widow's peak), anterior cranium bifidum occultum, median facial cleft affecting the nose, upper lip, and/or palate, and uni- or bilateral clefting of the ala nasi. The anomalies noted in FNM may be explained as a single malformation. If the nasal capsule fails to develop properly, the primitive brain vesicle fills the space normally occupied by the capsule, thus producing anterior cranium bifidum occultum, an arrest in the positioning of the eyes, and a lack of formation of the nasal tip. The condition presents clinically with variable expressions as sporadic cases and infrequently in familial cases. The present study is the first attempting to quantify and characterize FNM via anatomic radiographic measurements. The lateral (LA) and posterior-anterior

(PA) cephalometric radiographs of twenty-four individuals, both sporadic and familial, with FNM were analyzed for comparison of linear and angular measurements with previously published data of a "normal," i.e. unaffected, population standard. Usual and customary cephalometric points were identified and located, then digitized into the computer. Twenty-nine measurements included the previously diagnosed anomalous features of hypertelorism, medial nasal cavity, and palatal shelves, as well as other facial features. The radiographs of individuals with FNM have anatomic features that are unusual and distinct to the specific malformation. The data from this research suggest that patients with FNM, regardless of a genetic or sporadic predisposition, have a midface deficiency in height and depth, an increased interorbital width with possible increased orbital socket width, and a longer zygomatic buttress. Also, the familial cases tend to have a flatter cranial base than the sporadic cases. Furthermore, the familial patients might be a different type of FNM since this subgroup shows narrower zygomatic widths. The patients with surgical procedures demonstrated improvement different from the growth of those patients who did not have surgery. The hypothesis that the facies of a patient with frontonasal malformation is different from the "normal" control population is supported by this research. The differences between the familial and sporadic patients tend to support the general theory that genetic predisposition is less severe than FNM that occurs randomly.

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